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December 27, 2013

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Assessment
eCTD Sequence Number: 0007

Dear Drug Master File Staff:

This Type V DMF contains the Risk Evaluation and Mitigation Strategy (REMS) for Transmucosal Immediate Release Fentanyl for the Shared System REMS program.

Included in this submission, please find the REMS Assessment 3 at 24 months.

McKesson states that information provided in this Master File is current and assures that the material furnished will meet the specifications described herein. McKesson also confirms that the Holder obligations are observed.

We request that all information in this file be treated as confidential commercial information to the Food and Drug Administration pursuant to 21 C.F.R. §20.61, and that no information from this file be provided to any unauthorized persons without written consent.

If you have any questions or concerns, please do not hesitate to contact Jann Kochel, U.S. Agent for McKesson, at 610-535-6500, ext. 5572 or alternatively via email at jann.a.kochel@accenture.com.

Sincerely,

Jann A. Kochel, U.S. Agent
Accenture, LLP
585 East Swedesford Road
Wayne, PA 19087

Attachments: Table of Contents for the submission
Electronic Submission Specifications

Assessment – 24 Months

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments Administrative Information Page
1.16 – Risk Management Plans	REMS History REMS Assessment – 24 Months

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway. This eCTD has been generated by Accenture, LLP (formerly Octagon Research Solutions Inc.), who has filed an acceptable eCTD pilot with the Center (Pilot Number 900777).

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
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Statement of Commitment: Attached, please find a signed statement of commitment. The statement certifies that the DMF is current and that McKesson will comply with the statements made in it.

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Modification No.	Date Approved	Documents Affected	Overview of Modification
1	June 5, 2012	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient Provider Agreement Form • Patient and Caregiver Overview • Dear Healthcare Provider Letter • Outpatient Pharmacy Overview • Chain Pharmacy Overview • Inpatient Pharmacy Overview • Outpatient Pharmacy Enrollment Form • Chain Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Outpatient Pharmacy Letter • Inpatient Pharmacy Letter • Dear Distributor Letter • Distributor Enrollment Form • Supporting Document	**Sequence 0002**: Edits to Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form*, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray) and minor editorial changes. *The Closed System Pharmacy Enrollment Form was not formally submitted through the Gateway but was submitted via email on May 18, 2012 and included in the June 5, 2012 FDA approval letter.
N/A	N/A	Assessment Report 1 at 6 months – due 06/28/2012	**Sequence 0003**: Assessment report covering 12/28/2011 to 04/27/2012
2	November 7,	Draft Documents	**Sequence 0004**:

	2013	submitted on or before 09/28/2012 • Chain Pharmacy Enrollment Form • Outpatient Pharmacy Enrollment Form • Closed System Pharmacy Overview • Education Program • Frequently Asked Questions (FAQ) • Outpatient Pharmacy Letter • REMS • Supporting Document	Modification proposed to: • Incorporate closed system pharmacies into the TIRF REMS Access Program • Correct minor inconsistencies between the FDA provided versions and the current PDF versions of REMS materials
N/A	N/A	Assessment Report 2 at 1 year – due 12/28/2012	**Sequence 0005**: Assessment report covering 04/28/2012 to 10/28/2012
2	November 7, 2013	Amendment to 09/28/2012 supplement: • Chain Outpatient Pharmacy Enrollment Form • Independent Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment Form • Distributor Enrollment Form • Prescriber Enrollment Form • Patient Provider Agreement Form • Chain Outpatient	**Sequence 0006**: Modification proposed to: • Revised terminology, processes, and definitions for outpatient pharmacies • Revised attestations for physicians and patients to address concerns regarding patient access • Revised Program Overview and Frequently Asked Questions to improve clarity and content • Updated REMS materials to reflect the completion of the transition phase for the TIRF REMS Access Program

		Pharmacy Overview • Independent Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Patient and Caregiver Overview • Prescriber Overview • Education Program • Knowledge Assessment • Frequently Asked Questions (FAQ) • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Healthcare Provide Letter • Dear Distributor Letter • REMS • Supporting Document • Website Landing Page	
N/A	N/A	Assessment Report 3 at 2 years – due 12/28/2013	**Sequence 0007: Assessment report covering 10/29/2012 to 10/28/2013**

Title: Transmucosal Immediate-Release Fentanyl (TIRF)
Risk Evaluation and Mitigation Strategy (REMS) Access Program
24-month Assessment Report

Reporting Timeframe: 29OCT2012 to 28OCT2013

Document Number: Final v1.0 – 18DEC2013

Product Name: Transmucosal Immediate-Release Fentanyl

Sponsor: TIRF REMS Industry Group (TRIG) of Companies:

Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
Depomed, Inc.
Galena Biopharma, Inc.
Insys Therapeutics Inc.
Mallinckrodt Pharmaceuticals
Meda Pharmaceuticals, Inc.
Mylan, Inc.
Par Pharmaceutical, Inc.

Confidentiality Statement

The information contained herein is confidential and the proprietary property of the TRIG of Companies and its affiliates, and any unauthorized use or disclosure of such information without the prior written authorization of the TRIG is expressly prohibited.

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LIST OF ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
AERS	Adverse Event Reporting System
ANDA	Abbreviated New Drug Application
BTP	Breakthrough Pain
CSR	Call Center Service Representative
DEA	Drug Enforcement Administration
ETASU	Elements to Assure Safe Use
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
KAB	Knowledge, Attitude, and Behavior
MedDRA	Medical Dictionary for Drug Regulatory Activities
NC	Non-Compliant
NCPDP	National Council for Prescription Drug Program
NDA	New Drug Application
NDC	National Drug Code
NPI	National Provider Identifier
NCRT	Non-Compliance Review Team
PMS	Pharmacy Management System
PPAF	Patient-Prescriber Agreement Form
PT	Preferred Terms
REMS	Risk Evaluation and Mitigation Strategy
REMS edits	Checks conducted by the TIRF REMS Access program to confirm that all safety requirements were met
SMQ	Standardized MedDRA Query
SOP	Standard Operating Procedure
TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl product(s)
TIRF REMS Access	REMS program for TIRF medicines
TIRF Sponsors	The group of sponsors that are submitting this REMS
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

EXECUTIVE SUMMARY

The Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program was approved by the Food and Drug Administration (FDA) on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS® and generic versions of these TIRF medicines. On 04 January 2012, the FDA approved the inclusion of SUBSYS® to the TIRF REMS Access Program. The TIRF REMS Access Program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval. The initial REMS Assessment report was submitted on 28 June 2012 (cut-off date of 27 April 2012). The second REMS Assessment Report covered the period from 27 April 2012 to 28 October 2012. This third REMS Assessment Report (24 months) covers the period from 29 October 2012 to 28 October 2013.

Prescribers

Prescriber enrollment in the TIRF REMS Access Program during the current reporting period totaled 2,001 newly enrolled prescribers and 938 re-enrollments.

A total of 1,259 prescribers were inactivated in this reporting period, with 99.8% due to expiration of their enrollment period and 0.2% because the prescribers were deceased. As part of the REMS requirements, prescribers must re-enroll every 2 years.

During the reporting period, a total of 325 incomplete Prescriber Enrollment Forms were received. The majority of incomplete forms were due to missing physician signature and date (86.8%).

Pharmacies

During the current reporting period, 22,762 pharmacies including 22,744 non-closed system pharmacies and 18 closed system pharmacy locations enrolled in the TIRF REMS Access Program. Of the non-closed system pharmacy enrollments, 1,944 were new enrollments and 20,800 were re-enrollments. For closed system pharmacies, all were newly enrolled. As part of the REMS requirements, pharmacies must re-enroll every 2 years.

A total of 184 incomplete Pharmacy Enrollment Forms were received. Forms were received both via fax and via Web. The most frequently reported reasons for incomplete faxed enrollment forms were Knowledge Assessment Failure (n=16, 8.7%), invalid National Counsel for Prescription Drug Programs (NCPDP) number (n=6, 3.3%), pending test transaction verification (n=6, 3.3%). Other reasons for incomplete enrollment forms include invalid Drug Enforcement Agency (DEA) number (n=5, 2.7%), invalid National Provider Identifier (NPI) number (n=5, 2.7%). It should be noted that each form may have multiple reasons and could have been submitted multiple times.

A total of 2,493 non-closed system pharmacies were inactivated due to expiration of their enrollment period in the TIRF REMS Access Program, representing 21 inpatient pharmacies, (0.8%), 2,470 outpatient pharmacies (99.1%), and 2 chain pharmacies (0.1%).

There were 675 outpatient pharmacies that attempted to configure a pharmacy management system (PMS) to electronically submit prescriptions to REMS edits. Of these, 645 (95.6%) successfully configured their systems in this reporting period; the mean number of days to

successfully configure their systems was 0.61 days (min/max; 0.0001 days/203.85 days). The 203.85 day outlier for the PMS configuration was an independent outpatient pharmacy that submitted their first PMS test transaction on 18 December 2012 and completed the last PMS test transaction on 10 July 2013 due to the pharmacy's decision to delay enrollment in the TIRF REMS Access Program.

Wholesalers/Distributors

In addition, 13 wholesaler/distributors enrolled during the current reporting period including 9 wholesaler/distributors that re-enrolled. There were 4 wholesalers/distributors inactivated during the reporting period due to expiration of enrollment but 2 had re-enrolled by the end of the reporting period.

Patients

During the current reporting period, 7,767 patients were enrolled in the TIRF REMS Access Program. Because patients are passively enrolled with their first prescription, they are not required to re-enroll at any point. Instead, prescribers must renew a patient PPAF every 2 years. No patients were inactivated from the TIRF REMS Access Program during this reporting period.

A total of 111,104 prescriptions were adjudicated for safety by the TIRF REMS Access Program in the current reporting period including 110,170 prescriptions from non-closed system pharmacies and 934 from closed system pharmacies. Of the total prescriptions, 94.0% were subsequently approved for dispensing (meaning authorized for dispensing by insurance or cash bin). There were 1,140 patients who received prescriptions for a TIRF medicine from 3 or more prescribers in a rolling 6-month period. Patients may have multiple prescribers for various reasons such as patient relocation, prescriber relocation/retirement/death, or patient is seen at a single practice with multiple prescribers.

A total of 8,256 prescriptions were dispensed to 7,064 patients during the first 10 days after patient enrollment (i.e., enrollment occurred when first prescription was filled). There were a greater number of patients who had their initial prescription filled in the first 10 days without a Patient-Prescriber Agreement Form (PPAF) compared with those patients with a PPAF (77.2% vs. 20.0%). For patients without a PPAF, the majority of patients (77%) received only 1 fill.

A total of 15,536 prescription claims were rejected due to failure to meet REMS requirements for the prescriber and/or patient and/or pharmacy. A single prescription may have been submitted and rejected multiple times. The majority of rejection reasons were due to the prescriber not enrolled or the prescriber ID not being found in the TIRF REMS Access database (43.6%), patient zip code missing from claim (18.8%), PPAF incomplete (15.2%), prescriber last name did not match name registered (14.5%), and pharmacy not enrolled (7.8%). Definitions are provided in Section 5.2.4.

The TIRF REMS Access Program Call Center was contacted most frequently for the following reasons: inquiring about a pharmacy claim rejection (15.99%), enrollment status inquiry (14.19%), PPAF status inquiry (12.75%), and general program questions (8.01%).

During the current reporting period, the TIRF REMS Access Program received 1 report of difficulty accessing an enrolled prescriber. This situation occurred as a result of an enrolled

prescriber assisting a patient who was relocating and needed to identify an enrolled prescriber in his/her new location.

FDA Adverse Event Reporting System

Since the last TIRF REMS Assessment Report, 16 FDA Adverse Event Reporting System (FAERS) case reports in the United States (US) were associated with a TIRF medicine exposure. Eight (8) of the cases included one of the individual Preferred Terms (PT) of Interest for the TIRF REMS or at least one PT from the Medical Dictionary for Drug Regulatory Activities (MedDRA) standardized MedDRA Query (SMQ), *Acute Central Respiratory Depression*.

American Association of Poison Control Centers

There were 17 cases of exposure to known oral fentanyl immediate-release medicines reported to the American Association of Poison Control Centers (AAPCC) during the current reporting period. Two deaths were reported for exposures to TIRF medicines. There was 1 pediatric/adolescent exposure (age 16) reported for TIRF medicines with a medical outcome of minor effect.

Twenty cases of exposure to unknown fentanyl were reported to the AAPCC during the current reporting period. The cases had medical outcomes of 2 deaths (indirect reports), 3 major effects, 8 moderate effects, 3 minor effects, 3 unable to follow/judged as potentially toxic exposure, and 1 no effect. Both cases with the outcome of death were classified as intentional abuse. There were 4 reports characterized as intentional suspected suicide, all of these patients survived. No pediatric exposures in children under 16 years of age were reported.

In compliance with the FDA's request in January 2013, the TIRF Sponsors will provide the AAPCC fatality abstracts for the 7 deaths reported in the 12-Month Assessment Report as soon as they are available. AAPCC fatality abstracts are generally available in the 3rd or 4th quarter following the year of interest. The TIRF Sponsors will share these fatality abstracts with FDA via email at the earliest date possible. The TIRF Sponsors will share information on the deaths reported in this assessment report when they become available in 2014.

Knowledge, Attitudes, and Behavior (KAB) Surveys

During the 12-month reporting period TRIG determined that a correct response rate of 65% or greater would be considered to represent adequate understanding of each concept or key risk message. The same criterion was applied to the 24-month KAB surveys. The purpose of establishing this threshold was to assist TRIG in tracking and monitoring the level of understanding of key risk messages across each wave to determine if the goals of the REMS are being met and if any modification to the REMS is required.

In the 24-month patient survey, 2 concepts had correct response rates of less than 65% which include the need to stop taking TIRF medicines if around-the-clock opioid medications are stopped and the approved indication for TIRF medicines for patients. The first concept of stopping a TIRF medicine if an around the clock opioid is discontinued was also a low scoring item in the prescriber survey. The TRIG is exploring options to increase awareness of this important safety message.

Overall, given the results of the remaining items/questions throughout the 6 key risk messages this survey indicates that patients are knowledgeable about the safe use and storage of TIRF medicines. The higher level of understanding in patients who read most or all of the Medication Guide demonstrates effective communication of the key risk messages, which may also be reinforced by prescribers and pharmacists. The consistent high level of patient understanding of key risk messages between the 12-month and 24-month surveys indicates that the REMS goals are being met with the tools currently in place. As demonstrated in appended KAB report there were no important differences in the correct response rates for most the key risk messages between the 12-month and 24-month assessments.

In the 24-month pharmacist survey, only one item was identified as having a low level of understanding among pharmacists (TIRF medicines are not indicated for chronic non-cancer pain; 47.0% responded correctly). However, it should be noted that there was a marked improvement in the Pharmacist's correct response rate for this concept from the 12-month KAB survey to the 24-month KAB survey. It should also be noted that recognition of uses for which TIRF medicines are not indicated is not a goal of the TIRF REMS for pharmacists. The overall high level of understanding of all other items that comprise the 4 key risk messages indicates that the current education program for pharmacists is meeting the REMS goals. The vast improvement in the correct response rate between the 12-month assessment and 24-month assessment provides further evidence that the educational program has been effective at significantly increasing pharmacists' knowledge regarding safe use of TIRF medicines. Thus, no changes to the pharmacist education program are required at this time.

In the 24-month prescriber survey, there were no significant differences in correct response rates for most questions in each of the key risk messages between the 12-month and 24-month assessments. The 2 questions that elicited higher rates of correct responses in the 24-month survey were added as key risk message questions for the 24-month survey. These Questions (found in appended KAB report) are related to the concept of opioid-tolerant patients.

The concept that a patient must discontinue a TIRF medicine when they stop taking their around-the-clock opioid, while not a key risk message for the prescribers, received a low correct response rate. Prescribers are educated on this concept in the Education Program and in the PPAF. Prescribers low understanding of this concept is likely to have affected the level of understanding of respondents in the patient survey.

The overall higher level of understanding of the remaining items/questions throughout the 4 key risk messages indicates that prescribers are knowledgeable about the safe of TIRF medicines. The consistent high level of prescribers' understanding of key risk messages between the 12-month and 24-month surveys indicates that the Prescriber Education Program is meeting the goals of the TIRF REMS Access Program with the tools currently in place.

1 BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended release and immediate-release products. Extended-release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain.

Transmucosal immediate-release fentanyl products ("TIRF medicines") and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' the chronic pain control (breakthrough pain, BTP). All the TIRF medicines are short-acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with the use and misuse of TIRF medicines, including acute respiratory depression which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose and prescribing to opioid-non-tolerant patients have led to serious and on occasion fatal, adverse events demonstrating that short-acting fentanyl products can pose a health risk if not used appropriately.

The FDA has determined that a REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program was approved by the FDA on 28 December 2011. The group of Sponsors that are submitting this REMS includes (Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics Inc., Mallinckrodt Pharmaceuticals, Meda Pharmaceuticals, Mylan, Inc. and Par Pharmaceutical, Inc.) are hereafter referred to as the TIRF Sponsors. During this reporting period, Depomed, Inc. acquired the New Drug Application (NDA) for LAZANDA from Archimedes Pharma US, Inc., who is no longer a TIRF Sponsor. In addition, Galena Biopharma, Inc., acquired the NDA for ABSTRAL from Prostrakan Inc. and is now a TIRF Sponsor (as of 01 May 2013) whereas ProStrakan subsequently exited the group. Additionally, Mylan became a TIRF Sponsor on 29 May 2013 due to a pending Abbreviated New Drug Application (ANDA). The TIRF REMS Access Program is administered by McKesson Specialty Health and RelayHealth. This report is prepared by United BioSource Corporation (UBC).

The TIRF medicines that are the subject of this TIRF REMS are shown in Table 1 below.

Table 1: TIRF Medicines

Product Name (active ingredient)/formulation
NDA 022510, ABSTRAL (fentanyl) sublingual tablets
NDA 020747, ACTIQ (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 021947, FENTORA (fentanyl buccal tablet)
NDA 022569, LAZANDA (fentanyl) nasal spray
NDA 022266, ONSOLIS (fentanyl), buccal soluble film
NDA 202788, SUBSYS (fentanyl sublingual spray)
ANDA 077312, fentanyl citrate oral transmucosal lozenge
ANDA 078907, fentanyl citrate oral transmucosal lozenge

The TIRF REMS Access Program addresses the current requirements set forth by the FDA and provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

The initial REMS was approved on 28 December 2011 and went live on 12 March 2012. The FDA required an initial report 6 months after REMS approval; therefore, the first report was submitted on 28 June 2012 with a cut-off date of 27 April 2012. The 12-month report was submitted on 28 December 2012 with a cut-off date of 28 October 2012. For this reporting period the cut-off date was 28 October 2013 thereby allowing 60 days to prepare this report for the FDA, which is due on 28 December 2013.

2 REMS GOALS

The goals of the TIRF REMS Access Program are to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors are executing the TIRF REMS Access Program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access Program including patients, prescribers, pharmacies and distributors must be enrolled in the TIRF REMS Access Program, educated on the requirements of the program and required to document that they understand and will abide by the "elements to assure safe use."

Program materials are provided on the TIRF medicines in addition to product-specific materials. The Education Program and Knowledge Assessment components of the program contain both TIRF medicine class and product-specific components. All program tools, including enrollment forms, PPAFs, stakeholder letters, and overview documents containing program information specific to the TIRF REMS Access Program, are available through www.TIRFREMSACCESS.com.

The program procedures are monitored for adherence and the TIRF Sponsors will continue to conduct ongoing and retrospective analyses as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

3.1 Additional Elements

3.1.1 Medication Guide

The product-specific TIRF Medication Guide should be dispensed with each TIRF medicine prescription. Every TIRF medicine has a unique Medication Guide.

3.1.2 Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS was not required. However, TIRF Sponsors sent materials to targeted stakeholders to support implementation of the TIRF REMS Access Program at the time of program launch. These communications included Dear Healthcare Provider and Dear Pharmacy letters, and informed prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access Program and means of reporting adverse events. In this reporting period, there were no mailings of either the Dear Healthcare Provider or Dear Pharmacy letters.

3.2 Elements to Assure Safe Use (ETASU)

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This is achieved by each prescriber's enrollment through a review of the TIRF REMS Access Education Program including the TIRF medicine's Full Prescribing Information, successful completion of the Knowledge Assessment, and completion of the enrollment form.

TIRF medicines are only available through the TIRF REMS Access Program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies that dispense TIRF medicines must be enrolled into the TIRF REMS Access Program. There are

different enrollment requirements for outpatient pharmacies (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and inpatient pharmacies (e.g., hospitals that dispense for inpatient use only). For Long-Term Care and Hospice patients whose prescriptions were obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access Program.

Implementation of the TIRF REMS Access Program for closed system pharmacies was launched on 30 June 2012. Closed system pharmacies are integrated healthcare systems that dispense for outpatient use but their pharmacy management systems are unable to support the process of electronically transmitting the validation and claim information.

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to review of the TIRF REMS Access Education Program, successfully complete the Knowledge Assessment and submit a completed and signed TIRF REMS Access Program enrollment form. The authorized pharmacist ensures that their PMS is able to support communication with the TIRF REMS Access Program using established telecommunication standards. This requires submitting standardized validation test transactions to validate the system enhancements. The authorized pharmacist is also responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access Program. This training is documented by the pharmacy.

For inpatient pharmacy enrollment, the authorized pharmacist is required to review the TIRF REMS Access Education Program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist is required to acknowledge that they understand that outpatient pharmacies within their facility must be enrolled separately.

For chain pharmacies, an authorized chain pharmacy representative completes the enrollment process on behalf of all individual store locations associated with that chain. The authorized chain pharmacy representative acknowledges that training has been provided to all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment have been completed, the authorized chain pharmacy representative, on behalf of the chain, is required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access Program requirements by submitting a completed and signed enrollment form.

The reasons and description for stakeholder incomplete enrollments are described in Section 5.2.2 and Section 5.2.3.

Patients are passively enrolled in the TIRF REMS Access Program when their first prescription is processed by a pharmacy. A completed PPAF should be sent to the TIRF REMS Access Program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of 3 prescriptions are allowed within 10 working days from the date that the patient had their first prescription filled. No further prescriptions are to be dispensed after the 10 working day window until a completed PPAF is received. A patient's healthcare provider can submit a copy of the PPAF to the TIRF REMS Access Program via the Web site, fax, or US mail.

3.2.1 Prescription Verification

Following initial patient enrollment upon processing of a patient's first TIRF medicine prescription, pharmacies verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access Program and that all REMS requirements are met prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

Specific reasons why a prescription would not meet a REMS edit are described in Section 5.2.4.

Non-Closed System Pharmacies

Prescription verification occurs through a model that uses a pharmacy billing claim and engages a switch provider in the validation process.

Upon receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the prescription details are entered into their PMS and a transaction is sent to the TIRF REMS Access Program via a switch provider. If the patient is not enrolled and this is their first prescription, the TIRF REMS Access Program uses this transaction data to automatically transfer patient details into the TIRF REMS Access database for passive enrollment.

For all prescriptions, the REMS database is then interrogated, via the switch provider, to validate the REMS edits (i.e., confirm that all TIRF REMS Access Program requirements are met).

In the case where a prescription passes all REMS edits, a billing request is then sent to the payer by the switch provider. Once the payer authorizes payment, the switch provider then authorizes the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which is captured by the TIRF REMS Access Program.

If the prescription does not pass all REMS edits (e.g., one of the stakeholders was not enrolled), the TIRF REMS Access Program rejects the claim prior to the claim being forwarded to the payer and the pharmacy receives a rejection notice from the switch provider. This automated feedback indicates the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notifies the pharmacist to contact the TIRF REMS Access Program Call Center for further information.

Closed System Outpatient Pharmacies

Upon receipt of a prescription for a TIRF medicine at an enrolled closed system outpatient pharmacy, a pharmacy staff member will contact the TIRF REMS Access Program via phone or fax to provide prescription details for verification. The TIRF REMS Access Program then validates the enrollment status for the patient, prescriber and pharmacy. If the patient is not enrolled, the TIRF REMS Access Program will use this transaction information to automatically transfer patient details into the TIRF REMS Access database for passive enrollment. If all three stakeholders are enrolled (i.e. passes all REMS edits), the closed system outpatient pharmacy is given an authorization number which is captured by the TIRF REMS Access Program. If the prescription does not pass all REMS edits (e.g., one of the stakeholders is not enrolled), the TIRF REMS Access Program will not provide an authorization number and the closed system outpatient pharmacy will receive a rejection notice. This feedback will be provided to the closed system outpatient pharmacy via phone or fax and will include the reason for rejection,

information on how the rejection may be resolved and instructions to not dispense the TIRF prescription until resolution is reached.

3.3 Implementation System

The Implementation System and its components are described in the following sections.

3.3.1 Wholesaler/Distribution Enrollment and Fulfillment

Wholesalers/distributors who distribute TIRF medicines must be enrolled in the TIRF REMS Access Program before they are allowed to distribute TIRF medicines.

For the purpose of the TIRF REMS Access Program, the term distributor refers to wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors received a Dear Distributor Letter describing the TIRF REMS Access Program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies upon FDA approval of the program. To enroll, the distributor's authorized representative must review the distributor program materials, complete and sign the Distributor Enrollment Form and fax it to the TIRF REMS Access Program. TIRF Sponsors have processes in place to prevent shipping TIRF medicines to any distributor who has not completed and signed the enrollment form.

3.3.2 The TIRF REMS Access Program Compliance

The TIRF REMS Access Program Non-Compliance Review Team (NCRT) was created by the TRIG on 19 October 2012 and is tasked with reviewing reports of suspected non-compliance with the TIRF REMS Access Program requirements. The NCRT is composed of membership from all TRIG sponsors. There are currently 23 individuals across the 8 sponsors; the functional areas or specialties represented by the members include Regulatory, Medical Affairs, REMS Specialist, Legal, Quality and Drug Safety.

TIRF Sponsors monitor prescriber, inpatient and outpatient pharmacy, and wholesaler/distributor activities for compliance with TIRF REMS Access Program requirements. Corrective actions (e.g., re-education, additional monitoring, process revision, stakeholder inactivation) are instituted by the TIRF Sponsors as appropriate if non-compliance is confirmed. The Non-Compliance Plan is described in Section 4.2 and results of non-compliance investigations are included in Section 6 of this report.

3.3.3 TIRF REMS Access Program Call Center

The TIRF REMS Access Program includes a Call Center component. The Call Center is staffed by qualified and trained specialists, who provide TIRF REMS Access Program support to patients, prescribers, pharmacies, and distributors.

4 REMS ASSESSMENT PLAN METHODS

The aim of the TIRF REMS Access Program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access Program to ensure safe use,

proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations are used to identify ways to improve the processes, as needed.

Based on communications between TRIG and the FDA, new metrics were proposed by the FDA on 19 September 2013. Some of the metrics require further evaluation and clarification with the FDA prior to implementation. Those metrics that had been provided to the FDA in the 10 October 2013 communication from the TRIG are included in this report. Many of these metrics were the same as those provided in the 12-month report, but were stratified by closed system and non-closed system pharmacy. One metric is indicated as new. The metrics cross referenced to the FDA's 9/19/2013 list are shown in Tables 2 through 6.

4.1 Data Sources

Data were collected from the following main sources as described in detail below: a) the TIRF REMS Access Program outreach (Section 4.1.1), b) TIRF REMS Access product and program utilization statistics (Section 4.1.2), c) program infrastructure and performance (Section 4.1.3), and d) safety surveillance (Section 4.1.4). All programmed source tables and histograms, as well as source data are on file at UBC and available upon request. The individual metrics for each main data source are provided below with a direct link to the results sections of the report.

4.1.1 TIRF REMS Access Program Outreach

The following metrics were tabulated for this reporting period to assess program outreach efforts (Section 5.1.1):

Table 2: TIRF REMS Access Program Outreach Metrics

Metric Number Indicated in RSD	Metric Number Indicated in FDA Assessment Plan 9/19/2013	Metric
1.	1.a	Number of Dear HCP letters mailed to prescribers (by date)
2.	1.b.	Number of returned mailings of Dear HCP letters to prescribers.
3.	1.c.	Number of Pharmacist letters mailed to pharmacies (by date)
4.	1.d.	Number of returned mailings of Pharmacist letters to pharmacies

4.1.2 The TIRF REMS Access Program and Product Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers, the following metrics were tabulated for this reporting period and cumulatively:

Table 3: Currently Approved Metrics and New Metrics – Utilization Statistics

Metric Number Indicated in RSD	Metric Number Indicated in FDA Assessment Plan 9/19/2013	Metric
5.	n/a	Number of new patients enrolled by state (Section 5.2.1)
6.	n/a	Number of patients inactivated (Section 5.2.1)
7.	n/a	Number of attempts needed for prescribers to successfully complete Knowledge Assessments (Section 5.2.2) • Method of completion
8.	n/a	Number of new prescribers enrolled by state (Section 5.2.2) • Method of enrollment • Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
9.	n/a	Number of prescribers who are inactivated (Section 5.2.2)
10.	2.c.i	Number of new pharmacies enrolled by type, by state (Section 5.2.3) • Method of enrollment • Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
11.	2.c.iii	Number of pharmacies that are inactivated by type (Section 5.2.3)
12.	n/a	Number of attempts needed for pharmacies to successfully complete Knowledge Assessments (Section 5.2.3)
13.	2.e	Dispensing activity for enrolled outpatient pharmacies (Section 5.2.4) • Total number of prescriptions authorized • Total number of prescriptions rejected for safety (description of safety issues and any interventions or corrective actions taken)
14.	n/a	Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome) (Section 5.2.4)
15.	2.d.ii	Number of wholesalers/distributors inactivated, total (Section 5.2.5)
16.	2.d.i	Number of new wholesalers/distributors enrolled (Section 5.2.5) • Method of enrollment • Number of incomplete forms, to extent possible, a brief description of the reason for incomplete data fields
17.	n/a	Number of days between enrollment and receipt of a PPAF (Section 5.2.6) • Method of PPAF submission
18.	2 f 2.g.	Number of prescriptions dispensed per patient during the first 10 days after patient enrollment with and without a PPAF in place stratified by open and closed system pharmacies. (Section 5.2.6) • A histogram of the number of days between passive enrollment and receipt of a PPAF. Stratify by the method of PPAF submission

Table 3: Currently Approved Metrics and New Metrics – Utilization Statistics

Metric Number Indicated in RSD	Metric Number Indicated in FDA Assessment Plan 9/19/2013	Metric
		• A histogram of the number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment stratified by whether there is a PPAF in place. • **(new)** The number of prescriptions dispensed after 10 days without a PPAF in place stratified by open and closed system pharmacies

n/a indicates metric is not included in the 9/19/2013 FDA Assessment Plan.

4.1.3 Program Infrastructure and Performance

The following metrics on program infrastructure performance were tabulated for this reporting period and cumulatively:

Table 4: Currently Approved Metrics and New Metrics-Program Infrastructure and Performance

Metric Number Indicated in RSD	Metric Number Indicated in FDA Assessment Plan 9/19/2013	Metric
19.	n/a	Assessment of process for pharmacies to upgrade their PMS (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems) (Section 5.3.1)
20.	3.a.	Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem) (Section 5.3.2)
21.	3.c.ii. 3.c.iii.	Call center report (Section 5.3.3) • Summary of frequently asked questions • Problems reported
22.	3.d.	Description of corrective actions taken to address program/system problems (Section 5.4)
23.	n/a	Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area (Section 5.4.1)
24.	n/a	Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays (Section 5.4.2)

n/a indicates metric is not included in the 19 September 2013 FDA Assessment Plan.

The following reports for unintended system interruptions were provided for this reporting period:

Table 5: New Metrics

Metric Number Indicated in RSD	Metric Number Indicated in FDA Assessment Plan 9/19/2013	Metric
25.	n/a	Reports identified of inadvertent enrollment deactivations (Section 5.5.1)
26.	n/a	Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code) (Section 5.5.2)
27.	n/a	Reports of failure of re-enrollment notifications to reach stakeholders (Section 5.5.3)
28.	n/a	Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection (Section 5.5.4)

n/a indicates metric is not included in the 9/19/2013 FDA Assessment Plan.

Table 6: Additional Metrics Requested by the FDA

Metric Number Indicated in RSD	Metric Number Indicated in FDA Assessment Plan 9/19/2013	Metric
n/a	3.e.i.	The number of duplicate prescribers, patients, and pharmacies identified in the system.
n/a	3.e.ii	Why the duplications were not originally detected.
n/a	3.e.iii.	The corrective actions taken to assure minimization of future duplicative data entries

4.1.4 Safety Surveillance

TIRF Sponsors processed adverse event reports related to their specific products and reported to the FDA according to current regulations outlined in 21 CFR 314.80 and the respective sponsors' Standard Operating Procedures (SOPs).

Surveillance data from the following sources are included in the REMS Assessment Report:

- FDA Adverse Event Reporting System (FAERS) database using signal detection methods for TIRF medicines to identify outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion. See Appendix 12.1 for list of MedDRA Preferred Terms used.
- AAPCC (Appendix 12.2) data for TIRF medicines and unknown fentanyl products with inhalation or ingestion as routes of exposure.

4.2 TIRF REMS Access Program Non-Compliance Plan

The TIRF REMS Access Program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the Non-Compliance Plan is to help TRIG identify and investigate deviations from and non-compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program. A confirmed non-compliant (NC) event is when the information collected through investigation of the potential NC event clearly indicates that a program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified.

The TIRF REMS Access Program routinely monitors stakeholder activity to identify potential incidents of non-compliance with program requirements. The TIRF REMS Access Program investigates all reports of suspected non-compliance. Routine monitoring of stakeholder activity includes, but is not limited to, the types identified in Table 7. Non-compliance information is collected through standard program reports, spontaneous reports identified via the program's call center, vendor/sponsor reported events, outreach to relevant stakeholders to validate data/information and solicit further information, investigation of the TIRF REMS Access database. The data are tracked through a NC case that is opened on the stakeholder record in the TIRF REMS Access database. Table 7 indicates each defined non-compliance activity and the method of monitoring.

Table 7 Non-Compliance Activity Monitoring

Stakeholder	Scenario	
	#	Non-Compliance Activity
Pharmacy	1	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF pharmacy management system that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.
	2	Dispensing activity for enrolled outpatient pharmacies during reporting period not matching distributor shipment data for that pharmacy.
	3	Pharmacy is dispensing TIRF medicine while suspended or deactivated from the TIRF REMS Access Program.
	4	[Placeholder for additional scenario if needed]
	5	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS Access Program.
	6	Inpatient Pharmacy dispenses for outpatient use
	7	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)
Wholesaler/ Distributor	1	Wholesaler/Distributor is suspended or deactivated from the TIRF REMS Access Program and is purchasing or distributing TIRF medicines.
	2	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.
Prescriber	1	Prescriber is prescribing TIRF medicines while suspended or deactivated from the TIRF REMS Access Program.

Table 7 Non-Compliance Activity Monitoring

Stakeholder	Scenario	
	2	Prescriber failure to submit completed PPAFs in a timely manner (5 or more enrolled patients without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date).
Closed System Pharmacy	1	Dispensing prescriptions outside of the closed system authorization process.
Patient	1	The Patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction
All Stakeholders	1	ENROLLMENT MONITORING ONLY: Monitor stakeholders who are not enrolled in TIRF and are associated with non-compliance cases.

If a non-compliance event is confirmed, additional investigation is conducted to determine the scope, impact, and root cause of the event. Stakeholders are notified of the investigation via a formal letter from the TIRF REMS Access Program (see section 4.2.1 below) and may also be requested to develop a corrective action plan. All corrective action plans are reviewed and approved by the NCRT.

The NCRT will determine if the Non-Compliance Protocol should be modified as the program evolves. Any changes to the plan proposed by the NCRT will be voted upon by the TRIG.

4.2.1 Corrective Action Measures

Decisions are made through the NCRT based on the severity of the action as well as the information collected during the investigation. Stakeholders that fail to comply with one or more elements of the TIRF REMS Access Program will be subject to corrective action. Appropriate corrective actions are determined by the TIRF REMS Access Program according to the severity of the event as defined below:

- Minor - An unintended (e.g., first-time) event. The corrective action typically involves a written notice to the stakeholder and re-education of the program requirements to prevent re-occurrences of the event.
- Moderate – Multiple occurrences of the same event or a series of distinct, unintended events.
- Serious - Continued events after retraining has occurred. This level of offense may result in a suspension from the program and possible deactivation.

Affected stakeholders are provided written notification of all confirmed non-compliance events. Corrective actions for confirmed events may include a Notice, Warning, Suspension, or Deactivation letter (See Table 8). If deemed necessary, temporary suspension of a prescriber, pharmacist or distributor from the TIRF REMS Access Program may be warranted, prohibiting them from prescribing, dispensing or distributing TIRF medicines for a certain period of time. The most severe consequence of a non-compliance event is deactivation, resulting in the

stakeholder not being able to receive/prescribe/dispense/distribute TIRF medicines and is applicable to all stakeholders including patients.

Formal notifications of non-compliance are sent by the TIRF REMS Access Program to the applicable prescriber and/or pharmacy whereas notices for patient non-compliance events are sent to their prescriber. Copies of notices sent to an individual chain pharmacy store are also sent to the chain pharmacy's headquarters.

Table 8: Corrective Action Guideline

Event Classification	Description
Notices	• Patient notices will be sent to a patient's prescriber • Minor violations that demonstrate a misunderstanding of the program requirements • Notices are intended to re-educate stakeholders • 2 Notices in 60 days = Review by Non-Compliance Review Team to determine if escalation to Warning is warranted
Warnings	• 2 Warnings in 60 days = Review by Non-Compliance Review Team to determine if escalation to Suspension is warranted • >1 Warning in >60 days = Case-by-Case review for Suspension
Suspension	• Temporary suspension from the program • A suspended pharmacy or distributor may keep existing TIRF inventory but may not purchase or acquire additional TIRF medicines • Pharmacies may not dispense TIRF medicines from existing inventory and distributors may not sell/distribute TIRF medicines during suspension • If the pharmacy or distributor is part of a larger entity that entity will be notified of the suspension • 1 Warning or 2 Notices in Suspension = Review by Non-Compliance Review Team to determine if escalation to Deactivation is warranted • 2 Suspensions Within a 12-Month Period = Review by Non-Compliance Review Team to determine if a Deactivation is warranted
Deactivation	• Deactivation may result from multiple failures to comply with the program elements and/or a non-compliance event for which there is no feasible corrective action • Bars stakeholder from providing TIRF medicines for their patients • Pharmacies and distributors must return all existing TIRF medicine • Patient deactivation will be sent to a patient's prescriber. Patients may only be reinstated into the program by a request from their prescriber

5 RESULTS

5.1 TIRF REMS Access Program Outreach

5.1.1 Dear Healthcare Professional Letters [Metric 1-4]

There were no mailings in this reporting period.

5.2 REMS Program Utilization

Described in this section are the total numbers and geographic distribution of all enrolled stakeholders (prescribers, patients, distributors, outpatient independent and inpatient pharmacies, corporate chain pharmacy offices and chain pharmacy stores), as well as stakeholder inactivations, dispensing activities, and barriers or delays in patient access.

5.2.1 Patient Enrollment [Metric 5 and 6]

During the current reporting period, there were 7,767 newly enrolled patients. Because patients are passively enrolled with their first prescription there is no patient re-enrollment, but prescribers are required to renew PPAFs with patients every 2 years. There were no patients inactivated during the reporting period.

New enrollments represented 49 states (Vermont had no patients enrolled), the District of Columbia and the Virgin Islands (Table 9). The following states had the highest proportion of enrolled patients: California (10.8%), Michigan (7.3%), Florida (7.1%), Texas (6.1%), New Jersey (4.0%), New York (3.9%), Alabama (3.5%), and Pennsylvania (3.0%). For 25.8% of the newly enrolled patients, the territory/state was unknown due to the patient not providing consent for use of this data by the TIRF REMS Access Program or because the patient did not have a PPAF on file. For patients who complete more than one PPAF, the location is recorded from the first completed PPAF received.

Table 9: Patient Enrollment and Geographic Distribution

	Current Reporting Period 29OCT2012 to 28OCT2013	**Cumulative[a,b] 28DEC2011 to 28OCT2013**
Parameter	N (%)	N (%)
Number of Enrolled Patients	7,767[c]	19,501
State/Territory of Patient Primary Address[d]		
Unknown	2,000 (25.8%)	3,514 (18.0%)
Alabama	268 (3.5%)	555 (2.9%)
Alaska	10 (0.1%)	42 (0.2%)
Arizona	111 (1.4%)	296 (1.5%)
Arkansas	72 (0.9%)	139 (0.7%)
California	835 (10.8%)	2,391 (12.3%)

Table 9: Patient Enrollment and Geographic Distribution

	Current Reporting Period 29OCT2012 to 28OCT2013	**Cumulative[a,b] 28DEC2011 to 28OCT2013**
Parameter	N (%)	N (%)
Colorado	117 (1.5%)	395 (2.0%)
Connecticut	81 (1.0%)	235 (1.2%)
Delaware	13 (0.2%)	66 (0.3%)
Florida	548 (7.1%)	1,495 (7.7%)
Georgia	105 (1.4%)	376 (1.9%)
Hawaii	2 (<0.1%)	20 (0.1%)
Idaho	22 (0.3%)	46 (0.2%)
Illinois	61 (0.8%)	341 (1.8%)
Indiana	71 (0.9%)	252 (1.3%)
Iowa	3 (<0.1%)	34 (0.2%)
Kansas	44 (0.6%)	139 (0.7%)
Kentucky	28 (0.4%)	104 (0.5%)
Louisiana	26 (0.3%)	76 (0.4%)
Maine	13 (0.2%)	25 (0.1%)
Maryland	74 (1.0%)	303 (1.6%)
Massachusetts	37 (0.5%)	136 (0.7%)
Michigan	563 (7.3%)	931 (4.8%)
Minnesota	14 (0.2%)	50 (0.3%)
Mississippi	79 (1.0%)	150 (0.8%)
Missouri	56 (0.7%)	184 (0.9%)
Montana	8 (0.1%)	24 (0.1%)
Nebraska	18 (0.2%)	51 (0.3%)
Nevada	40 (0.5%)	124 (0.6%)
New Hampshire	48 (0.6%)	74 (0.4%)
New Jersey	314 (4.0%)	970 (5.0%)
New Mexico	3 (<0.1%)	20 (0.1%)
New York	299 (3.9%)	923 (4.7%)
North Carolina	107 (1.4%)	424 (2.2%)
North Dakota	1 (<0.1%)	13 (0.1%)
Ohio	163 (2.1%)	445 (2.3%)
Oklahoma	90 (1.2%)	245 (1.3%)
Oregon	28 (0.4%)	115 (0.6%)
Pennsylvania	229 (3.0%)	633 (3.3%)
Rhode Island	69 (0.9%)	109 (0.6%)
South Carolina	76 (1.0%)	185 (1.0%)
South Dakota	3 (<0.1%)	7 (<0.1%)
Tennessee	170 (2.2%)	395 (2.0%)

Table 9: Patient Enrollment and Geographic Distribution

	Current Reporting Period 29OCT2012 to 28OCT2013	**Cumulative[a,b] 28DEC2011 to 28OCT2013**
Parameter	N (%)	N (%)
Texas	472 (6.1%)	1,353 (6.9%)
Utah	123 (1.6%)	317 (1.6%)
Vermont	0	1 (<0.1%)
Virginia	80 (1.0%)	266 (1.4%)
Washington	135 (1.7%)	338 (1.7%)
West Virginia	18 (0.2%)	51 (0.3%)
Wisconsin	12 (0.2%)	81 (0.4%)
Wyoming	4 (0.1%)	31 (0.2%)
District of Columbia	3 (<0.1%)	8 (<0.1%)
Puerto Rico	0	2 (<0.1%)
Virgin Islands	1 (<0.1%)	1 (<0.1%)

[a] Includes patients that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[b] Cumulative patients from the end of prior period may differ from last period's report due to reconciliation of duplicate patients.

[c] Patients enrolled in this time period and were still enrolled at the end of the time period.

[d] Patients are classified by state based on 5-digit zip code provided on PPAF. If the zip code is invalid, the patient's self-reported state is used if available.

Based upon FDA request, this report includes the proportion of each states' population enrolled as a TIRF REMS patient, as calculated using the number of patients in that state divided by the total population of that state as per the latest US census data (Table 10).

The highest proportion of patients enrolled according to state population were in the states of Alabama (0.0116%), Utah (0.0115%), New Jersey (0.0110%), Rhode Island (0.0104%), Michigan (0.0094%), Florida (0.0080%), Colorado (0.0079%), Delaware (0.0074%), Oklahoma (0.0065%), California (0.0064%), and Tennessee (0.0062%).

Table 10: Patient Enrollment by State According to 2010 US Census

State\Territory of Patient Primary Address[a]	Current Reporting Period[b] 29OCT2012 to 28OCT2013	Cumulative[b] 28DEC2011 to 28OCT2013	Population Derived from 2010 US Census Data[c]	Percentage of Population Enrolled in TIRF REMS Access[d]	Rate of Persons Enrolled (Per 100,000)[d]
Total	7,767	19,501	312,471,327	0.00006%	0.06
Unknown	2,000	3,514	N/A	N/A	N/A
Alabama	268	555	4,779,736	0.0116%	11.6
Alaska	10	42	710,231	0.0059%	5.9
Arizona	111	296	6,392,017	0.0046%	4.6
Arkansas	72	139	2,915,918	0.0048%	4.8
California	835	2,391	37,253,956	0.0064%	6.4
Colorado	117	395	5,029,196	0.0079%	7.9
Connecticut	81	235	3,574,097	0.0066%	6.6
Delaware	13	66	897,934	0.0074%	7.4
Florida	548	1,495	18,801,310	0.0080%	8.0
Georgia	105	376	9,687,653	0.0039%	3.9
Hawaii	2	20	1,360,301	0.0015%	1.5
Idaho	22	46	1,567,582	0.0029%	2.9
Illinois	61	341	12,830,632	0.0027%	2.7
Indiana	71	252	6,483,802	0.0039%	3.9
Iowa	3	34	3,046,355	0.0011%	1.1
Kansas	44	139	2,853,118	0.0049%	4.9
Kentucky	28	104	4,339,367	0.0024%	2.4
Louisiana	26	76	4,533,372	0.0017%	1.7
Maine	13	25	1,328,361	0.0019%	1.9
Maryland	74	303	5,773,552	0.0052%	5.2
Massachusetts	37	136	6,547,629	0.0021%	2.1
Michigan	563	931	9,883,640	0.0094%	9.4

Table 10: Patient Enrollment by State According to 2010 US Census

State\Territory of Patient Primary Address[a]	Current Reporting Period[b] 29OCT2012 to 28OCT2013	Cumulative[b] 28DEC2011 to 28OCT2013	Population Derived from 2010 US Census Data[c]	Percentage of Population Enrolled in TIRF REMS Access[d]	Rate of Persons Enrolled (Per 100,000)[d]
Minnesota	14	50	5,303,925	0.0009%	0.9
Mississippi	79	150	2,967,297	0.0051%	5.1
Missouri	56	184	5,988,927	0.0031%	3.1
Montana	8	24	989,415	0.0024%	2.4
Nebraska	18	51	1,826,341	0.0028%	2.8
Nevada	40	124	2,700,551	0.0046%	4.6
New Hampshire	48	74	1,316,470	0.0056%	5.6
New Jersey	314	970	8,791,894	0.0110%	11.0
New Mexico	3	20	2,059,179	0.0010%	1.0
New York	299	923	19,378,102	0.0048%	4.8
North Carolina	107	424	9,535,483	0.0044%	4.4
North Dakota	1	13	672,591	0.0019%	1.9
Ohio	163	445	11,536,504	0.0039%	3.9
Oklahoma	90	245	3,751,351	0.0065%	6.5
Oregon	28	115	3,831,074	0.0030%	3.0
Pennsylvania	229	633	12,702,379	0.0050%	5.0
Rhode Island	69	109	1,052,567	0.0104%	10.4
South Carolina	76	185	4,625,364	0.0040%	4.0
South Dakota	3	7	814,180	0.0009%	0.9
Tennessee	170	395	6,346,105	0.0062%	6.2
Texas	472	1,353	25,145,561	0.0054%	5.4
Utah	123	317	2,763,885	0.0115%	11.5
Vermont	0	1	625,741	0.0002%	0.2
Virginia	80	266	8,001,024	0.0033%	3.3

Table 10: Patient Enrollment by State According to 2010 US Census

State\Territory of Patient Primary Address[a]	Current Reporting Period[b] 29OCT2012 to 28OCT2013	Cumulative[b] 28DEC2011 to 28OCT2013	Population Derived from 2010 US Census Data[c]	Percentage of Population Enrolled in TIRF REMS Access[d]	Rate of Persons Enrolled (Per 100,000)[d]
Washington	135	338	6,724,540	0.0050%	5.0
West Virginia	18	51	1,852,994	0.0028%	2.8
Wisconsin	12	81	5,686,986	0.0014%	1.4
Wyoming	4	31	563,626	0.0055%	5.5
District of Columbia	3	8	601,723	0.0013%	1.3
Puerto Rico	0	2	3,725,789	0.0001%	0.1
Virgin Islands	1	1	106,405	0.0009%	0.9

N/A = not applicable

[a] Patients are classified by state based on 5-digit zip code provided on PPAF.

[b] Patients enrolled in this time period and were still enrolled at the end of the time period.

[c] Based on 2010 US Census Data

[d] Rates are based on Cumulative enrollment.

5.2.2 Prescriber Enrollment, Inactivation, and Education [Metric 7, 8, 9]

During the current reporting period, there were 2,001 newly enrolled prescribers and 938 prescribers who re-enrolled. (Table 12). The majority of these prescribers (71.3%) enrolled using the Web-based enrollment system. All other prescribers completed their enrollment manually and submitted it via fax (28.7%).

Enrolled prescribers represented all 50 states, the District of Columbia and Puerto Rico, The highest enrolling state was California (12.0%), followed by New York (10.7%), Florida (7.2%), New Jersey (6.8%), Texas (5.1%), and Pennsylvania (4.7%); all other states had enrollment of less than 4.0% of total prescribers.

During this reporting period, 325 incomplete Prescriber Enrollment Forms were received for prescribers who enrolled via fax (Table 13). Multiple forms may have been submitted for the same prescriber, and a form may be incomplete for more than one reason. The most frequent reason for an incomplete form submitted via fax was missing physician signature and date (n=282, 86.8%).

Prescribers who enroll via Web are required to complete a series of online modules and, at any given time in the process, one or more modules may be incomplete. A prescriber must complete all modules and requirements to become authorized to prescribe TIRF medicines. Of the 131 prescribers who initiated enrollment via the Web and had not completed enrollment as of the last date of the current reporting period (28 October 2013), the reasons for incomplete Web enrollment were as follows:

- no attestation (n=117, 89.3%)
- training not complete (n=97, 74.0%)

Web enrollment can be incomplete for more than one reason; therefore the total is greater than 100%.

Reasons for incomplete Web enrollment and the definitions are below.

Table 11: Reasons for Incomplete Prescriber Web Enrollment

Reason for Incomplete Enrollment	Description
Training Not Complete	When a stakeholder does not complete the Education Program, they will be incomplete for the reason of “Training Not Complete.”
No Attestation	When a stakeholder does not attest to their enrollment on the Web, they will be incomplete for the reason of “No Attestation.” Attestation is an e-signature and requires input of the date and checking the attestation check box on the Web.

Table 12: Prescriber Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative[a] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Total Number of Enrolled Prescribers	2,939[b]	10,718 [c]
Number of Newly Enrolled Prescribers	2,001 (68.1%)	9,672 (90.2%)
Number of Re-Enrolled Prescribers	938 (31.9%)	1,046 (9.8%)
Method of Successful New Enrollments[d]		
Web	2,095 (71.3%)	5,962 (55.6%)
Fax	844 (28.7%)	1,237 (11.5%)
One-time file upload	0	3,519 (32.8%)[c]
State/Territory of Prescriber Primary Address[e]		
Alabama	41 (1.4%)	140 (1.3%)
Alaska	4 (0.1%)	24 (0.2%)
Arizona	80 (2.7%)	315 (2.9%)
Arkansas	16 (0.5%)	68 (0.6%)
California	353 (12.0%)	1,359 (12.7%)
Colorado	65 (2.2%)	248 (2.3%)
Connecticut	35 (1.2%)	147 (1.4%)
Delaware	13 (0.4%)	38 (0.4%)
Florida	211 (7.2%)	694 (6.5%)
Georgia	72 (2.5%)	270 (2.5%)
Hawaii	3 (0.1%)	17 (0.2%)
Idaho	14 (0.5%)	34 (0.3%)
Illinois	115 (3.9%)	397 (3.7%)
Indiana	51 (1.7%)	264 (2.5%)
Iowa	10 (0.3%)	35 (0.3%)
Kansas	36 (1.2%)	90 (0.8%)
Kentucky	20 (0.7%)	83 (0.8%)
Louisiana	14 (0.5%)	99 (0.9%)
Maine	3 (0.1%)	23 (0.2%)
Maryland	109 (3.7%)	379 (3.5%)
Massachusetts	49 (1.7%)	180 (1.7%)
Michigan	63 (2.1%)	257 (2.4%)
Minnesota	29 (1.0%)	107 (1.0%)
Mississippi	21 (0.7%)	56 (0.5%)

Table 12: Prescriber Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative[a] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Missouri	18 (0.6%)	141 (1.3%)
Montana	8 (0.3%)	25 (0.2%)
Nebraska	33 (1.1%)	86 (0.8%)
Nevada	25 (0.9%)	94 (0.9%)
New Hampshire	10 (0.3%)	50 (0.5%)
New Jersey	201 (6.8%)	560 (5.2%)
New Mexico	4 (0.1%)	28 (0.3%)
New York	314 (10.7%)	802 (7.5%)
North Carolina	89 (3.0%)	406 (3.8%)
North Dakota	4 (0.1%)	15 (0.1%)
Ohio	77 (2.6%)	301 (2.8%)
Oklahoma	33 (1.1%)	102 (1.0%)
Oregon	40 (1.4%)	125 (1.2%)
Pennsylvania	137 (4.7%)	603 (5.6%)
Rhode Island	8 (0.3%)	24 (0.2%)
South Carolina	24 (0.8%)	95 (0.9%)
South Dakota	4 (0.1%)	9 (0.1%)
Tennessee	85 (2.9%)	318 (3.0%)
Texas	149 (5.1%)	689 (6.4%)
Utah	32 (1.1%)	146 (1.4%)
Vermont	1 (0.0%)	7 (0.1%)
Virginia	56 (1.9%)	238 (2.2%)
Washington	102 (3.5%)	296 (2.8%)
West Virginia	13 (0.4%)	37 (0.4%)
Wisconsin	29 (1.0%)	146 (1.4%)
Wyoming	7 (0.2%)	20 (0.2%)
District of Columbia	7 (0.2%)	28 (0.3%)
Puerto Rico	2 (0.1%)	3 (0.0%)
Distribution of Reasons for Incomplete Prescriber Enrollment Forms Received for Fax-Enrolled Prescribers[f,g]	325[h]	525[h]
Missing Physician Signature Date	282 (86.8%)	459 (87.4%)
Missing Signature	282 (86.8%)	459 (87.4%)
Missing Email	32 (9.9%)	83 (15.8%)
Missing NPI Number	62 (19.1%)	75 (14.3%)
Missing State License Number	50 (15.4%)	70 (13.3%)

Table 12: Prescriber Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative[a] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Invalid DEA Number	27 (8.3%)	57 (10.9%)
Provided DEA Number does not have Correct Schedule for this Drug	27 (8.3%)	56 (10.7%)
Invalid NPI Number	22 (6.8%)	43 (8.2%)
Missing DEA Number	33 (10.2%)	41 (7.8%)

Note: Percentages are based on the total number (N) of prescribers for the period except for counts of incomplete forms.

[a] Cumulative is defined as sum of consecutive reporting periods.

[b] Includes prescribers enrolled or re-enrolled during the reporting period and were still enrolled at the end of the time period.

[c] Includes prescribers who transitioned into the TIRF REMS Access Program from other individual REMS programs.

[d] Percentage is based on the number of prescribers new to the TIRF REMS Access Program, including prescribers that transitioned from other individual REMS programs.

[e] Enrolled prescribers are classified by their primary address as recorded on the Prescriber Enrollment Form.

[f] Percentage is based on the total number of incomplete forms received in the reporting period. Forms may be incomplete for more than one reason and more than one incomplete form received for a unique prescriber.

[g] Reflects only enrolled prescribers who completed enrollment via fax. Some stakeholders may have attempted enrollment via the Web.

[h] Does not include prescribers who transitioned into the TIRF REMS Access Program from other individual REMS programs.

A total of 1,259 prescribers were inactivated at some point during the current reporting period, and the majority of these (1,256, 99.8%) were due to expiration of enrollment period. It should be noted that a prescriber is required to enroll every 2 years within the TIRF REMS Access Program. Of those 1,256 prescribers whose enrollment period expired at some point during the current reporting period, 999 (79.5%) of these prescribers' statuses remained expired at the close of the reporting period (Table 13). Of these 999 prescribers, 854 (85.5%) had not issued a prescription within six months (May 1, 2013- October 28, 2013).

Table 13: Prescriber Inactivations

	Current Reporting Period[a] 29OCT2012 to 28OCT2013	Cumulative[b] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Number of Inactivated Prescribers	1,259	1,901

Table 13: Prescriber Inactivations

	Current Reporting Period[a] 29OCT2012 to 28OCT2013	Cumulative[b] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Reason(s) For Inactivation[c]		
Deceased	3 (0.2%)	7 (0.4%)
Program Opt-Out	0	6 (0.3%)
Enrollment Expired	1,256 (99.8%)	1,888 (99.3%)
Enrollment Expired at End of Period[d]	999 (79.5%)	1,529 (81.0%)

Note: Percentages are based on the total number (N) for the relevant stakeholder/period.

[a] Prescribers whose status is 'inactive' at least once during the reporting period.

[b] Cumulative is sum of all reporting period totals.

[c] Percentages are based on the total number (N) of inactivated prescribers. A prescriber may have more than one reason for inactivation.

[d] Prescribers whose status is 'Inactive – Expired" at any time during the enrollment period.

[e] Prescribers whose status is "Inactive – Expired" at the end of the period. Percentages are based on the total number (N) of prescribers with "Inactive – Expired" status at least once.

Among 2,949 prescribers who successfully completed the Knowledge Assessment during the reporting period, 68.1% completed the assessments via the Web and 31.9% completed them via fax (Table 14). (Note: Knowledge Assessments and enrollment may not have been completed in the same reporting period. Most prescribers passed the Knowledge Assessment on the first attempt (58.3%) or second attempt (25.7%). Fifty-one (1.8%) prescribers enrolled during this assessment period required more than 4 attempts to successfully complete the Knowledge Assessments. Thirteen prescribers successfully completed the Knowledge Assessment more than once during this reporting period).

Prescribers who are unable to successfully complete the Knowledge Assessment after 6 attempts are "suspended" in the TIRF REMS Access Program until a representative from the Call Center can conduct outreach to provide additional educational assistance. Eight prescribers were contacted during the reporting period due to failure to successfully complete the Knowledge Assessment after six attempts. These 8 prescribers have successfully completed the Knowledge Assessment.

Table 14: Enrolled Prescriber Completed Knowledge Assessments and Number of Attempts Needed to Complete

	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative[a,b] 28DEC2011 to 28OCT2013
Parameter[c]	**N (%)**	**N (%)**
Total Number of Successfully Completed Knowledge Assessments (KA) by Enrolled Prescribers[d]	2,949	7,255
Method of KA Completion		
Web	2,008 (68.1%)	5,744 (79.2%)
Fax	941 (31.9%)	1,511 (20.8%)
Number of Prescribers with One or More Attempts to Successfully Complete Knowledge Assessment[e]		
One attempt	1,718 (58.3%)	3,707 (51.1%)
Two attempts	759 (25.7%)	2,168 (29.9%)
Three attempts	310 (10.5%)	903 (12.5%)
Four attempts	111 (3.8%)	300 (4.1%)
Five attempts	31 (1.1%)	107 (1.5%)
Six attempts	12 (0.4%)	48 (0.7%)
Greater than six attempts	8 (0.3%)	22 (0.3%)

Note: Percentages are based on the total number (N) of prescribers successfully enrolled in the period.

a Cumulative stakeholders from the end of prior period may differ from last period's report due to reconciliation of duplicate stakeholders.

b Cumulative number does not include prescribers transitioned into the TIRF REMS Access Program from the individual REMS programs.

c Enrolled prescriber includes newly enrolled prescribers and prescribers who re-enrolled during the current reporting period.

d Limited to successfully enrolled prescribers completing a Knowledge Assessment.

e Prescribers may have completed more than one Knowledge Assessment.

5.2.3 Pharmacy Enrollment, Inactivation, and Education [Metric 10, 11, 12]

There was a total of 22,762 pharmacies newly enrolled or re-enrolled in this reporting period. Of the 1,962 pharmacies that newly enrolled in the TIRF REMS Access Program 1,944 were non-closed system pharmacies and 18 were closed system pharmacy locations. A total of 20,800 pharmacies re-enrolled, all of which were non-closed system pharmacies. Non-closed system pharmacies are comprised of corporate pharmacy stores (93.7%), independent outpatient

pharmacies (5.3%), inpatient pharmacies (0.9%), and corporate pharmacy headquarters (0.2%) and closed system pharmacies (0.1%) (Table 15).

The enrolled pharmacies represented all 50 states, as well as the District of Columbia and Puerto Rico. The states that had the highest proportion of total newly enrolled or re-enrolled pharmacies included California (8.5%), Florida (8.3%), New York (7.5%), Texas (5.6%), Illinois (4.5%), Pennsylvania (4.4%), Ohio (3.9%), North Carolina (3.6%), Georgia (3.6%), New Jersey (3.2%), and Michigan (3.2%); all other states had enrollment ≤2.9%.

As shown in Table 15, the method of enrollment for the majority of pharmacies was via their corporate chain headquarters (76.0%, i.e., enrollment occurred via file enrollment upload), and the others enrolled via the Web (22.6%), or manually by fax (1.4%).

A total of 184 incomplete Pharmacy Enrollment Forms were received. Forms were received both via fax and via Web. The most frequently reported reasons for incomplete faxed enrollment forms were Knowledge Assessment Failure (n=16, 8.7%), invalid National Counsel for Prescription Drug Programs (NCPDP) number (n=6, 3.3%), pending test transaction verification (n=6, 3.3%). Other reasons for incomplete enrollment forms include invalid Drug Enforcement Agency (DEA) number (n=5, 2.7%), invalid National Provider Identifier (NPI) number (n=5, 2.7%). It should be noted that each form may have multiple reasons and could have been submitted multiple times.

As described for prescribers, pharmacies that enroll via Web do not submit forms, but instead move through a series of online modules. At any given time in the process, one or more modules may be incomplete. Pharmacists or authorized pharmacy representatives must complete all modules and requirements to become authorized to dispense TIRF medicines. There were a number of outpatient pharmacies (N=198), inpatient pharmacies (N=35), and corporate pharmacy headquarters/stores (N=47) that initiated enrollment via the Web but had not completed enrollment as of the last date of the current reporting period (28 October 2013).

The most common reasons for incomplete Web enrollment are shown below. Enrollment can be incomplete for more than one reason therefore the total is greater than 100%.

The major reasons for incomplete Web enrollment of outpatient pharmacies (N=198) are listed below:

- no attestation (98, 49.5%),
- pending test transaction verification (97, 49.0%)
- training not complete (87, 43.9%)

The major reasons for incomplete Web enrollment of inpatient pharmacies (N=35) were:

- no attestation (35, 100.0%)

- invalid DEA number (8, 22.9%)

The major reasons for incomplete Web enrollment of corporate pharmacy stores (N=47) were:

- training not complete (47, 100.0%)
- invalid DEA number (6, 12.8%)

Reasons for Web incomplete enrollment and the definition are proved below.

Table 15: Reasons for Incomplete Pharmacy Web Enrollment

Reason for Incomplete Enrollment	Description
Training Not Complete	When a stakeholder does not complete the Education Program, they will be incomplete for the reason of "Training Not Complete."
No Attestation	When a stakeholder does not attest to their enrollment on the Web, they will be incomplete for the reason of "No Attestation." Attestation is an e-signature and requires input of the date and checking the attestation check box on the Web.
Pending Test Transaction	When an independent or chain outpatient pharmacy fails to complete the test transactions to enable their pharmacy management system to support communication with the TIRF REMS Access system.
Invalid DEA	When the enrolling stakeholder is not associated to the DEA number provided or enters an incorrect DEA number.

Table 16: Pharmacy Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Number of Enrolled Pharmacies[b]	22,744	18	22,762	38,455 [c]	332	38,787
Independent Outpatient	1,193 (5.3%)	N/A	1,193 (5.2%)	4,927 (12.8%)	N/A	4,927 (12.7%)
Corporate Pharmacy Headquarters	35 (0.2%)	N/A	35 (0.2%)	85 (0.2%)	N/A	85 (0.2%)
Corporate Pharmacy Stores	21,305 (93.7%)	N/A	21,305 (93.6%)	32,553 (84.7%)	N/A	32,553 (83.9%)
Inpatient	211 (0.9%)	N/A	211 (0.9%)	890 (2.3%)	N/A	890 (2.3%)
Closed System Pharmacies	N/A	18 (100.0%)	18 (0.1%)	N/A	332 (100.0%)	332 (0.9%)
Number of Re-Enrolled Pharmacies	20,800 (91.5%)	0	20,800 (91.4%)	20,849 (54.2%)	0	20,849 (53.8%)
Independent Outpatient	573 (2.8%)	N/A	573 (2.8%)	606 (2.9%)	N/A	606 (2.9%)
Corporate Pharmacy Headquarters	34 (0.2%)	N/A	34 (0.2%)	34 (0.2%)	N/A	34 (0.2%)
Corporate Pharmacy Stores	20,166 (97.0%)	N/A	20,166 (97.0%)	20,175 (96.8%)	N/A	20,175 (96.8%)
Inpatient	27 (0.1%)	N/A	27 (0.1%)	34 (0.2%)	N/A	34 (0.2%)
Method of Successful Enrollments[d]						
Web	5,129 (22.6%)	3 (16.7%)	5,132 (22.6%)	9,348 (24.3%)	27 (8.1%)	9,375 (24.2%)
Fax	320 (1.4%)	1 (5.6%)	321 (1.4%)	482 (1.3%)	7 (2.1%)	489 (1.3%)
File (file enrollment upload)	17,295 (76.0%)	14 (77.8%)	17,309 (76.0%)	28,625 (74.4%)	298 (89.8%)	28,923 (74.6%)
State/Territory of Pharmacy Primary Address[e]						
Alabama	362 (1.6%)	0	362 (1.6%)	644 (1.7%)	4 (1.2%)	648 (1.7%)
Alaska	38 (0.2%)	0	38 (0.2%)	51 (0.1%)	0	51 (0.1%)
Arizona	596 (2.6%)	0	596 (2.6%)	811 (2.1%)	2 (0.6%)	813 (2.1%)
Arkansas	127 (0.6%)	0	127 (0.6%)	260 (0.7%)	3 (0.9%)	263 (0.7%)
California	1,921 (8.5%)	0	1,921 (8.4%)	3,538 (9.2%)	82 (24.7%)	3,620 (9.3%)
Colorado	490 (2.2%)	0	490 (2.2%)	577 (1.5%)	30 (9.0%)	607 (1.6%)
Connecticut	296 (1.3%)	0	296 (1.3%)	497 (1.3%)	0	497 (1.3%)
Delaware	139 (0.6%)	0	139 (0.6%)	160 (0.4%)	1 (0.3%)	161 (0.4%)

Table 16: Pharmacy Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Florida	1,877 (8.3%)	0	1,877 (8.3%)	3,079 (8.0%)	18 (5.4%)	3,097 (8.0%)
Georgia	816 (3.6%)	2 (11.1%)	818 (3.6%)	1,392 (3.6%)	9 (2.7%)	1,401 (3.6%)
Hawaii	29 (0.1%)	0	29 (0.1%)	111 (0.3%)	14 (4.2%)	125 (0.3%)
Idaho	98 (0.4%)	0	98 (0.4%)	149 (0.4%)	1 (0.3%)	150 (0.4%)
Illinois	1,014 (4.5%)	0	1,014 (4.5%)	1,491 (3.9%)	8 (2.4%)	1,499 (3.9%)
Indiana	385 (1.7%)	0	385 (1.7%)	882 (2.3%)	4 (1.2%)	886 (2.3%)
Iowa	114 (0.5%)	0	114 (0.5%)	232 (0.6%)	0	232 (0.6%)
Kansas	160 (0.7%)	0	160 (0.7%)	288 (0.8%)	0	288 (0.7%)
Kentucky	337 (1.5%)	0	337 (1.5%)	501 (1.3%)	3 (0.9%)	504 (1.3%)
Louisiana	303 (1.3%)	0	303 (1.3%)	533 (1.4%)	2 (0.6%)	535 (1.4%)
Maine	159 (0.7%)	0	159 (0.7%)	204 (0.5%)	0	204 (0.5%)
Maryland	469 (2.1%)	2 (11.1%)	471 (2.1%)	796 (2.1%)	20 (6.0%)	816 (2.1%)
Massachusetts	485 (2.1%)	0	485 (2.1%)	866 (2.3%)	1 (0.3%)	867 (2.2%)
Michigan	738 (3.2%)	0	738 (3.2%)	1,435 (3.7%)	6 (1.8%)	1,441 (3.7%)
Minnesota	354 (1.6%)	0	354 (1.6%)	540 (1.4%)	0	540 (1.4%)
Mississippi	166 (0.7%)	0	166 (0.7%)	321 (0.8%)	2 (0.6%)	323 (0.8%)
Missouri	399 (1.8%)	0	399 (1.8%)	650 (1.7%)	4 (1.2%)	654 (1.7%)
Montana	47 (0.2%)	0	47 (0.2%)	97 (0.3%)	2 (0.6%)	99 (0.3%)
Nebraska	96 (0.4%)	0	96 (0.4%)	195 (0.5%)	0	195 (0.5%)
Nevada	167 (0.7%)	0	167 (0.7%)	314 (0.8%)	3 (0.9%)	317 (0.8%)
New Hampshire	151 (0.7%)	0	151 (0.7%)	201 (0.5%)	0	201 (0.5%)
New Jersey	719 (3.2%)	3 (16.7%)	722 (3.2%)	1,319 (3.4%)	4 (1.2%)	1,323 (3.4%)
New Mexico	125 (0.6%)	0	125 (0.6%)	175 (0.5%)	0	175 (0.5%)
New York	1,707 (7.5%)	0	1,707 (7.5%)	2,582 (6.7%)	5 (1.5%)	2,587 (6.7%)
North Carolina	818 (3.6%)	0	818 (3.6%)	1,270 (3.3%)	4 (1.2%)	1,274 (3.3%)
North Dakota	31 (0.1%)	0	31 (0.1%)	52 (0.1%)	1 (0.3%)	53 (0.1%)
Ohio	897 (3.9%)	0	897 (3.9%)	1,595 (4.2%)	15 (4.5%)	1,610 (4.2%)
Oklahoma	158 (0.7%)	0	158 (0.7%)	379 (1.0%)	3 (0.9%)	382 (1.0%)

Table 16: Pharmacy Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Oregon	347 (1.5%)	0	347 (1.5%)	436 (1.1%)	2 (0.6%)	438 (1.1%)
Pennsylvania	993 (4.4%)	0	993 (4.4%)	1,938 (5.0%)	12 (3.6%)	1,950 (5.0%)
Rhode Island	98 (0.4%)	2 (11.1%)	100 (0.4%)	166 (0.4%)	2 (0.6%)	168 (0.4%)
South Carolina	447 (2.0%)	0	447 (2.0%)	676 (1.8%)	3 (0.9%)	679 (1.8%)
South Dakota	25 (0.1%)	0	25 (0.1%)	54 (0.1%)	0	54 (0.1%)
Tennessee	563 (2.5%)	0	563 (2.5%)	906 (2.4%)	5 (1.5%)	911 (2.4%)
Texas	1,270 (5.6%)	8 (44.4%)	1,278 (5.6%)	2,603 (6.8%)	21 (6.3%)	2,624 (6.8%)
Utah	150 (0.7%)	0	150 (0.7%)	314 (0.8%)	1 (0.3%)	315 (0.8%)
Vermont	87 (0.4%)	0	87 (0.4%)	95 (0.3%)	0	95 (0.2%)
Virginia	653 (2.9%)	1 (5.6%)	654 (2.9%)	1,058 (2.8%)	14 (4.2%)	1,072 (2.8%)
Washington	605 (2.7%)	0	605 (2.7%)	805 (2.1%)	5 (1.5%)	810 (2.1%)
West Virginia	172 (0.8%)	0	172 (0.8%)	292 (0.8%)	4 (1.2%)	296 (0.8%)
Wisconsin	364 (1.6%)	0	364 (1.6%)	607 (1.6%)	3 (0.9%)	610 (1.6%)
Wyoming	40 (0.2%)	0	40 (0.2%)	68 (0.2%)	2 (0.6%)	70 (0.2%)
District of Columbia	30 (0.1%)	0	30 (0.1%)	94 (0.2%)	3 (0.9%)	97 (0.3%)
Guam	0	0	0	1 (<0.1%)	0	1 (<0.1%)
Puerto Rico	112 (0.5%)	0	112 (0.5%)	153 (0.4%)	3 (0.9%)	156 (0.4%)
Virgin Islands	0	0	0	2 (<0.1%)	1 (0.3%)	3 (<0.1%)
Number of Incomplete Pharmacy Enrollment Forms Received for Fax Enrolled Pharmacies[f]	184 [g]	0	184	317 [g]	0	317
Not Agreed to Terms and Conditions	0	0	0	127 (40.1%)	0	127 (40.1%)
Knowledge Assessment Failure - First Attempt	16 (8.7%)	0	16 (8.7%)	44 (13.9%)	0	44 (13.9%)
Missing DEA Number	2 (1.1%)	0	2 (1.1%)	25 (7.9%)	0	25 (7.9%)
Pending Test Txn Verification	6 (3.3%)	0	6 (3.3%)	24 (7.6%)	0	24 (7.6%)
Invalid DEA Number	5 (2.7%)	0	5 (2.7%)	21 (6.6%)	0	21 (6.6%)
Missing Pharmacist Signature Date	3 (1.6%)	0	3 (1.6%)	14 (4.4%)	0	14 (4.4%)
Missing Signature	3 (1.6%)	0	3 (1.6%)	14 (4.4%)	0	14 (4.4%)

Table 16: Pharmacy Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Invalid NPI Number	5 (2.7%)	0	5 (2.7%)	13 (4.1%)	0	13 (4.1%)
Invalid NCPDP Number	6 (3.3%)	0	6 (3.3%)	12 (3.8%)	0	12 (3.8%)
Missing NPI Number	2 (1.1%)	0	2 (1.1%)	11 (3.5%)	0	11 (3.5%)
Missing Pharmacy Phone Number	3 (1.6%)	0	3 (1.6%)	6 (1.9%)	0	6 (1.9%)
Missing NCPDP Number	1 (0.5%)	0	1 (0.5%)	5 (1.6%)	0	5 (1.6%)
Missing State License Number	1 (0.5%)	0	1 (0.5%)	5 (1.6%)	0	5 (1.6%)
Missing Address - City	1 (0.5%)	0	1 (0.5%)	4 (1.3%)	0	4 (1.3%)
Missing Address - State	1 (0.5%)	0	1 (0.5%)	4 (1.3%)	0	4 (1.3%)
Missing Address - Street	1 (0.5%)	0	1 (0.5%)	4 (1.3%)	0	4 (1.3%)
Missing Email	0	0	0	4 (1.3%)	0	4 (1.3%)
Missing Fax Number	1 (0.5%)	0	1 (0.5%)	2 (0.6%)	0	2 (0.6%)
Knowledge Assessment Failure - Second Attempt	0	0	0	1 (0.3%)	0	1 (0.3%)
Missing Pharmacist Phone Number	0	0	0	1 (0.3%)	0	1 (0.3%)

Note: Percentages are based on the total number (N) for stakeholders for the period.

[a] Cumulative pharmacies from the end of prior period may differ from last period's report due to reconciliation of duplicate records.

[b] Pharmacies that are enrolled in this time period and were still enrolled at the end of the time period.

[c] Includes pharmacies that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[d] Method Definitions: *Web* – enrollment occurred via program Web site; *Fax* – enrollment occurred via fax sent to the Call Center; *File* – enrollment occurred via custom file load (e.g. chain stores).

[e] Pharmacies are classified by the primary address for the Pharmacist in Charge as recorded on the enrollment form.

[f] Percentage is based on the total number of incomplete forms received in the reporting period. Forms may be incomplete for more than one reason.

[g] Does not include pharmacies that transitioned into the TIRF REMS Access Program from other individual REMS programs.

As shown in Table 17, there were a total of 2,493 non-closed system pharmacies inactivated at least once during the reporting period including 2,470 (99.1%) outpatient pharmacies, 21 (0.8%) inpatient pharmacies, and 2 (0.1%) chain pharmacies. There were no closed system pharmacies inactivated during this reporting period. The reasons for inactivation are described in the table below.

Table 17: Pharmacy Inactivations

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Number of Inactivated Pharmacies	2,493	0	2,493	2,499	0	2,499
Inpatient	21 (0.8%)	N/A	21 (0.8%)	23 (0.9%)	N/A	23 (0.9%)
Outpatient	2,470 (99.1%)	N/A	2,470 (99.1%)	2,474 (99.0%)	N/A	2,474 (99.0%)
Chain	2 (0.1%)	N/A	2 (0.1%)	2 (0.1%)	N/A	2 (0.1%)
Reason(s) for Inpatient Pharmacy Inactivation[c]						
Enrollment Expired	21 (100.0%)	N/A	21 (100.0%)	21 (91.3%)	N/A	21 (91.3%)
Program Opt-Out	0	0	0	2 (8.7%)	0	2 (8.7%)
Reason(s) for Outpatient Pharmacy Inactivation[d]						
Enrollment Expired	2,400 (97.2%)	N/A	2,400 (97.2%)	2,400 (97.0%)	N/A	2,400 (97.0%)
Program Opt-Out	70 (2.8%)	0	70 (2.8%)	74 (3.0%)	0	74 (3.0%)
Reason(s) for Chain Pharmacy Inactivation[e]						
Enrollment Expired	2 (100.0%)	0	2 (100.0%)	2 (100.0%)	0	2 (100.0%)
Reason(s) for CSP Inactivation[f]						

Table 17: Pharmacy Inactivations

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
None	N/A	0	0	N/A	0	0

Note: Closed System Pharmacies refers to integrated healthcare systems that dispense TIRF medicines for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required by the TIRF REMS Access Program.
[a] Pharmacies with 'inactive' status at least once during the period.
[b] Cumulative is sum of all “reporting period” totals.
[c] Percentages are based on the total number (N) of inactivated inpatient pharmacies. An inpatient pharmacy may have more than one reason for inactivation.
[d] Percentages are based on the total number (N) of inactivated outpatient pharmacies. An outpatient pharmacy may have more than one reason for inactivation.
[e] Percentages are based on the total number (N) of inactivated chain pharmacies. A chain pharmacy may have more than one reason for inactivation.
[f] Percentages are based on the total number (N) of inactivated closed system pharmacies. A closed system pharmacy may have more than one reason for inactivation.

Of the 22,762 pharmacies that completed initial enrollment or re-enrollment during this reporting period, a total of 1,463 authorized pharmacists/pharmacy representatives (including 2 closed system pharmacies) completed the Knowledge Assessment (Table 18). The majority of authorized pharmacists/pharmacy representatives completed the Knowledge Assessment on the first attempt (46.8%) or the second attempt (33.9%). Of the 1,463, 96 authorized pharmacists/pharmacy representatives required four or more attempts to successfully complete the knowledge assessment. Authorized pharmacists/pharmacy representatives who are unable to successfully complete the Knowledge Assessment after 6 attempts are "suspended" in the TIRF REMS Access Program until a representative from the Call Center can conduct outreach to provide additional educational assistance. As of the end of the reporting period, all 6 pharmacists that were unsuccessful after 6 attempts or greater had been contacted and subsequently became enrolled.

The number of authorized pharmacists is lower than the number of enrolled pharmacies since pharmacies that were transitioned from an individual REMS program were not required to complete the Knowledge Assessment. Also, an authorized pharmacist/pharmacy representative may have been in charge of more than one store. Additionally, the TIRF REMS Access Program does not manage the education of the chain pharmacy stores; this is done by the corporate chain headquarters.

Table 18: Enrolled Authorized Pharmacist/Pharmacy Representatives Successfully Completing Knowledge Assessments and Attempts Needed to Successfully Complete Knowledge Assessment

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacists N (%)**
Number of Authorized Pharmacist/Pharmacy Representatives Successfully Completing Knowledge Assessment[c]	1,461	2	1,463	4,715	8	4,723
Number of Authorized Pharmacists with One or More Attempts to Successfully Complete Knowledge Assessment[d]						
One attempt	683 (46.8%)	2 (100.0%)	685 (46.8%)	1,978 (42.0%)	6 (75.0%)	1,984 (42.0%)
Two attempts	496 (34.0%)	0	496 (33.9%)	1,728 (36.7%)	2 (25.0%)	1,730 (36.6%)
Three attempts	186 (12.7%)	0	186 (12.7%)	674 (14.3%)	0	674 (14.3%)
Four attempts	69 (4.7%)	0	69 (4.7%)	225 (4.8%)	0	225 (4.8%)
Five attempts	21 (1.4%)	0	21 (1.4%)	75 (1.6%)	0	75 (1.6%)
Six attempts	5 (0.3%)	0	5 (0.3%)	26 (0.6%)	0	26 (0.6%)
Greater than six attempts	1 (0.1%)	0	1 (0.1%)	9 (0.2%)	0	9 (0.2%)

Note: Percentages are based on the total number (N) of pharmacists for the period. Closed system pharmacies refers to integrated healthcare systems that dispense TIRF medicines for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required by the TIRF REMS Access Program.

[a] Includes pharmacies that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[b] Cumulative from the end of prior period may differ from last period's report due to reconciliation of duplicates.

[c] For chain pharmacies, the results only reflect completion by an authorized pharmacist or pharmacy representative at the corporate headquarters and may not include individual retail locations. Corporate pharmacies are required to attest that authorized pharmacists and/or pharmacy representatives at individual store locations will complete all applicable assessments to participate in the program.

[d] Limited to pharmacists who ultimately successfully completed the Knowledge Assessment.

5.2.4 Dispensing Activity [Metric 13 and 14]

A total of 111,104 prescriptions were adjudicated for safety by the TIRF REMS Access Program in the current reporting period including 110,170 prescriptions from non-closed system pharmacies and 934 from closed system pharmacies. Of the total prescriptions, 94% were subsequently approved for dispensing (meaning authorized for dispensing by insurance or cash bin).

Table 19: Prescriptions Authorized for Dispensing from Outpatient Pharmacies

	Current Reporting Period 29OCT2012 to 28OCT2013			Cumulative[a,b] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies N (%)**
Number of Authorized Prescriptions[b]	110,170	934	111,104	178,620	1,195	179,815
Number of Authorized Prescriptions Dispensed[c]	103,523 (94.0%)	919 (98.4%)	104,442 (94.0%)	167,945 (94.0%)	1,177 (98.5%)	169,122 (94.1%)

Note: Percentages are based on the total number (N) of authorized prescriptions for the period.
[a] Includes authorizations from pharmacies that transitioned into the TIRF REMS Access Program from other individual REMS programs.
[b] Prescription successfully adjudicated for safety (i.e., successful REMS edit).
[c] Indicates number of prescriptions that were adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or cash bin (bin number).

A total of 15,536 prescription claims were rejected because they failed to meet REMS requirements for prescriber and/or patient and/or pharmacy including 15,321 from non-closed system pharmacies and 215 from closed system pharmacies. Note that prescription claims does not equal the number of hard copy prescriptions presented at TIRF enrolled pharmacies because a single prescription may have been submitted and rejected multiple times. The majority of rejection reasons were due to prescriber not enrolled or prescriber ID not found in TIRF REMS Access database (43.6%), patient zip code missing from claim (18.8%), PPAF incomplete (15.2%), prescriber last name did not match name registered (14.5%), or pharmacy was not enrolled (7.8%). The definitions for the reasons why prescriptions do not meet REMS edit requirements are provided below in Table 20.

Table 20 Reasons for Prescriptions Not Meeting REMS Edit Requirement

Reason	Description
Prescriber ID Not Enrolled/ Not Found	Found the prescriber last name but not the NPI, DEA or State License Number or both prescriber last name and ID are not found
PPAF Incomplete	Patient's PPAF is in an incomplete status; the PPAF is missing information
Patient Zip Code Missing	Patient's zip code was not submitted on the transaction
Prescriber Last Name Did Not Match Name Registered	Prescriber last name on the transaction did not match the prescriber last name associated with the Prescriber ID
Pharmacy Not Enrolled	Pharmacy is not enrolled; the pharmacy has not completed the enrollment or re-enrollment process

Upon receiving an inbound call from a pharmacy provider, the TIRF REMS Access Program Call Center Service Representative (CSR) works to resolve the rejected transaction and to provide instructions on the corrective action needed to successfully process the transaction. Corrective action includes outreach and education to remedy rejected transaction processing.

Table 21: Total Number of Prescriptions Rejected for Safety

	Current Reporting Period[a] 29OCT2012 to 28OCT2013			Cumulative[a] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Number of Prescriptions Rejected	15,321	215	15,536	39,561	318	39,879
Reasons For Rejection[b]						
Pharmacy not enrolled	1,209 (7.9%)	0	1,209 (7.8%)	4,263 (10.8%)	0	4,263 (10.7%)
Pharmacy enrollment incomplete or expired	161 (1.1%)	2 (0.9%)	163 (1.0%)	590 (1.5%)	7 (2.2%)	597 (1.5%)
System unavailable due to maintenance	9 (0.1%)	0	9 (0.1%)	17 (<0.1%)	0	17 (<0.1%)
Prescriber ID not submitted on claim	209 (1.4%)	1 (0.5%)	210 (1.4%)	442 (1.1%)	1 (0.3%)	443 (1.1%)
Prescriber ID not in TIRF REMS Access database	6,634 (43.3%)	134 (62.3%)	6,768 (43.6%)	17,251 (43.6%)	193 (60.7%)	17,444 (43.7%)
Prescriber last name did not match name registered	2,233 (14.6%)	27 (12.6%)	2,260 (14.5%)	5,129 (13.0%)	36 (11.3%)	5,165 (13.0%)
Prescriber enrollment incomplete or expired	483 (3.2%)	6 (2.8%)	489 (3.1%)	828 (2.1%)	9 (2.8%)	837 (2.1%)
Prescriber enrollment incomplete or expired and prescriber last name mismatch	15 (0.1%)	0	15 (0.1%)	42 (0.1%)	0	42 (0.1%)
DOB missing from claim	10 (0.1%)	0	10 (0.1%)	37 (0.1%)	0	37 (0.1%)
Patient first name missing from claim	133 (0.9%)	0	133 (0.9%)	308 (0.8%)	0	308 (0.8%)
Patient last name missing from claim	13 (0.1%)	0	13 (0.1%)	66 (0.2%)	0	66 (0.2%)
Patient zip code missing from claim	2,901 (18.9%)	15 (7.0%)	2,916 (18.8%)	6,563 (16.6%)	30 (9.4%)	6,593 (16.5%)
Multiple patients found	1 (<0.1%)	1 (0.5%)	2 (<0.1%)	14 (<0.1%)	1 (0.3%)	15 (<0.1%)

Table 21: Total Number of Prescriptions Rejected for Safety

	Current Reporting Period[a] 29OCT2012 to 28OCT2013			Cumulative[a] 28DEC2011 to 28OCT2013		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Prescriber decision to deactivate patient	0	0	0	0	0	0
Patient inactive >= 6mos and must resubmit PPAF	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Patient deceased	0	0	0	0	0	0
Database failure	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
PPAF Incomplete	2,328 (15.2%)	33 (15.3%)	2,361 (15.2%)	7,634 (19.3%)	50 (15.7%)	7,684 (19.3%)
PPAF Terminated	340 (2.2%)	2 (0.9%)	342 (2.2%)	383 (1.0%)	2 (0.6%)	385 (1.0%)

Note: Percentages are based on the total number (N) of rejected prescriptions for the relevant period. *Rejected for Safety* is defined in this table to mean the prescription did not pass REMS edits.
[a] Includes patients that transitioned into the TIRF REMS Access Program from other individual REMS programs.
[b] A prescription may be rejected for more than one reason.

Patients with prescriptions from multiple prescribers within an overlapping time frame were assessed. Patients may have multiple prescribers for various reasons such as patient relocation, prescriber relocation/retirement/death, or patient is seen at a single practice with multiple prescribers. Attempts are made to research reports of patients with prescriptions from 3 or more prescribers in a rolling 6-month period. In this reporting period, there were 671 patients who received prescriptions for a TIRF medicine from 3 or more prescribers with a rolling 6-month period.

In the last reporting period, there were 505 patients who had 3 or more prescribers in a rolling 6-month period. A total of 505 cases were investigated and 504 were closed as not a non-compliant event:

- 387 patients visited multiple prescribers in the same practice;
- 108 patients changed practices at some point in their therapy.
- 5 patients were reviewed with the NCRT for suspected abuse/misuse. The NCRT did not find suspected abuse/misuse after review.
- 4 patients consistently visited 2 practices, but there were no overlapping prescriptions between the two practices.

Per communication with FDA dated 15 May 2013, 1 patient case from the 505 cases investigated could not be ruled out for potential doctor shopping. The patient saw 4 prescribers in different practices. The patient received 28 prescriptions for one branded product (2 different strengths) over a 12 ½ month period. One independent outpatient pharmacy filled all prescriptions. This case was investigated and closed as a potential non-compliance event; however non-compliance could not be confirmed due to patient privacy restrictions.

5.2.5 Wholesaler/Distributor Enrollment [Metric 15 and 16]

During the current reporting period, 4 wholesalers/distributors newly enrolled via fax in the REMS program and 9 (69.2%) re-enrolled. (Table 22).

There were 4 wholesalers/distributors inactivated during the current reporting period because the enrollment expired and 2 had not re-enrolled by the end of the reporting period. (Table 23).

Table 22: Wholesaler/Distributor Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013	**Cumulative[a,b] 28DEC2011 to 28OCT2013**
Parameter	**N (%)**	**N (%)**
Number of Wholesalers/Distributors Enrolled	13	44
Number of Newly Enrolled Wholesalers/Distributors	4 (30.8%)	35 (79.5%)
Number of Re-Enrolled Wholesalers/Distributors	9 (69.2%)	9 (20.5%)
Method of Enrollment		
Fax	13 (100.0%)	31 (70.5%)
File	0	13 (29.6%)
Number of Incomplete Wholesaler/ Distributor Enrollment Forms Received	0	0

Note: Percentages are based on the total number (N) for the relevant Wholesalers/Distributors for the period.

[a] Includes Wholesalers/Distributors that transitioned into the TIRF REMS Access Program from other individual REMS programs.

[b] Cumulative Wholesalers/Distributors from the end of prior period may differ from last period's report due to reconciliation of duplicate Wholesalers/Distributors.

Table 23: Wholesaler/Distributor Inactivations

	Current Reporting Period[a] 29OCT2012 to 28OCT2013	Cumulative[b] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Number of Inactivated Wholesalers/Distributors	4 (100%)	4 (100%)

[a] Includes Wholesalers/Distributors with "inactive" status at least once during the period.

[b] Cumulative is the sum of "reporting period" totals.

5.2.6 Barriers or Delays in Patient Access [Metric 17 and 18]

A total of 7,071 PPAFs were submitted to the REMS program either via the Web (64.4%) or by fax (35.7%) during the reporting period. Approximately 49% of PPAFs were received the same day or within 10 days (36.2% on the same day and 12.7% between 1 and 10 days) (Table 24 and Figure 1).

Table 24 Submission of Patient-Prescriber Agreement Forms to the REMS Program

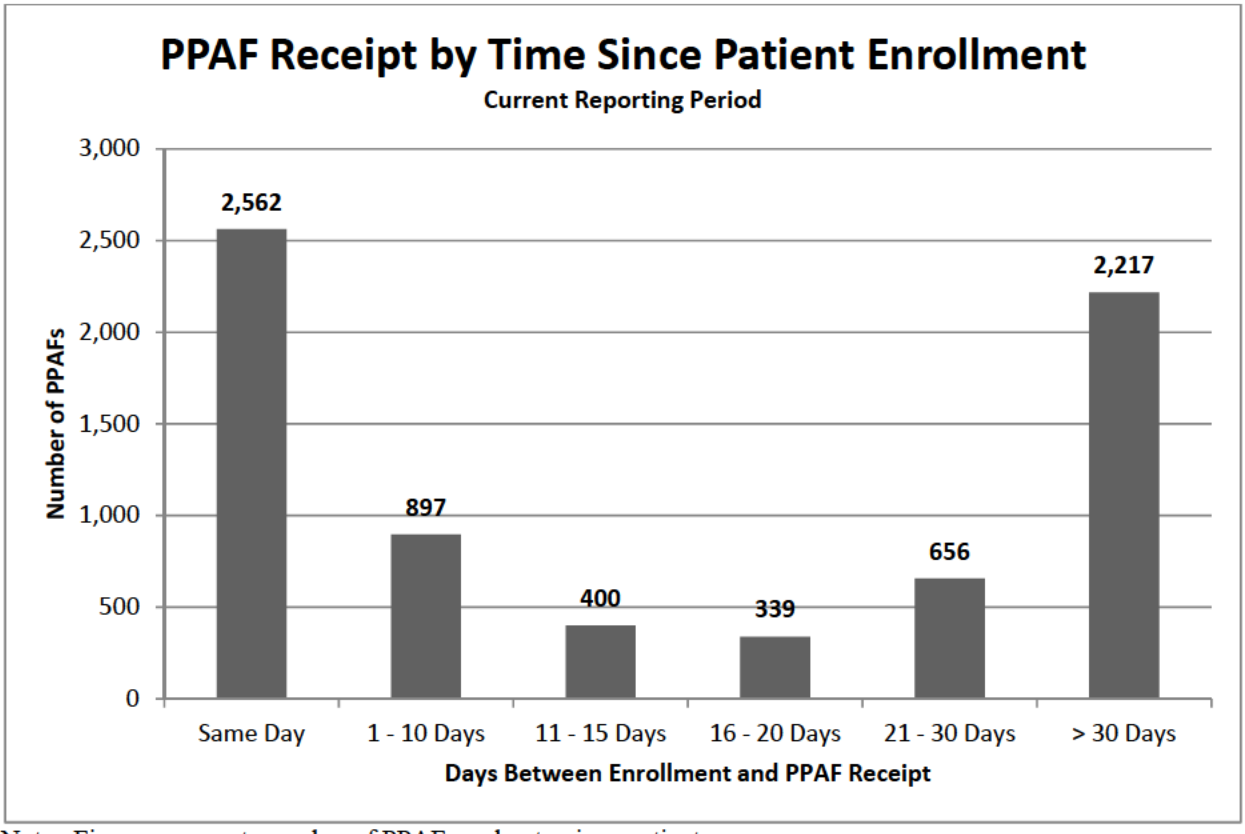
	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative[a, b] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Number of Patient-Prescriber Agreement Forms Submitted to REMS Program	7,071	16,518
Method of PPAF Submission		
Web	4,549 (64.4%)	11,331 (68.6%)
Fax	2,522 (35.7%)	4,799 (29.1%)
One-time file upload	0	388 (2.4%)
Number of Forms Received by Days Elapsed between Patient Enrollment and Receipt of Patient-Prescriber Agreement by REMS Program		
Form Received Same Day	2,562 (36.2%)	5,481 (33.2%)
Form Received between 1 and 10 days	897 (12.7%)	2,117 (12.8%)
Form Received between 11 and 15 days	400 (5.7%)	886 (5.4%)
Form Received between 16 and 20 days	339 (4.8%)	779 (4.7%)

Table 24 Submission of Patient-Prescriber Agreement Forms to the REMS Program

	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative[a, b] 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Form Received between 21 and 30 days	656 (9.3%)	3,092 (18.7%)
Form Received >30 days after Patient Enrollment	2,217 (31.4%)	4,163 (25.2%)

Note: Percentages are based on the total number (N) of forms for the period.
[a] Includes patients that transitioned into the TIRF REMS Access Program from other individual REMS programs.
[b] Cumulative total from the end of prior reporting period may differ from current period's report due to reconciliation of duplicates.

Figure 1: PPAF Receipt by Time Since Patient Enrollment (29OCT2012 to 28OCT2013)



Note: Figure represents number of PPAFs and not unique patients.

Within First 10 Days After Patient Enrollment

Across all pharmacies, a total of 8,256 prescriptions were dispensed to 7,064 patients within the first 10 days after patient enrollment (Table 25 and Figure 2 below). The majority of patients (7,008) were dispensed prescriptions by non-closed system pharmacies (8,180). The majority of patients (77.2%) received only 1 fill without a PPAF.

Table 25: Prescriptions Dispensed During the First 10 Days after Passive Patient Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013				Cumulative[a,b] 28DEC2011 to 28OCT2013			
Parameter	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined[d] Pharmacies N (%)**	**Filled at All Pharmacies N (%)**	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined[d] Pharmacies N (%)**	**Filled at All Pharmacies N (%)**
Number of prescriptions dispensed to patients during the first 10 days after patient enrollment	8,180	76	0	8,256	20,364	173	8	20,545
Number of patients dispensed a prescription during the first 10 days after patient enrollment	7,008	56	0	7,064	17,443	145	4	17,592
With PPAF[b]								
1 Fill	1,404 (20.0%)	6 (10.7%)	0	1,410 (20.0%)	2,662 (15.3%)	11 (7.6%)	1 (25.0%)	2,674 (15.2%)
2 Fills	194 (2.8%)	0	0	194 (2.7%)	411 (2.4%)	1 (0.7%)	0	412 (2.3%)
3 Fills	26 (0.4%)	0	0	26 (0.4%)	61 (0.3%)	0	0	61 (0.3%)
>3 Fills	5 (0.1%)	1 (1.8%)	0	6 (0.1%)	17 (0.1%)	1 (0.7%)	0	18 (0.1%)

Table 25: Prescriptions Dispensed During the First 10 Days after Passive Patient Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013				Cumulative[a,b] 28DEC2011 to 28OCT2013			
Parameter	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined[d] Pharmacies N (%)**	**Filled at All Pharmacies N (%)**	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined[d] Pharmacies N (%)**	**Filled at All Pharmacies N (%)**
Without PPAF[b,c]								
1 Fill	5,409 (77.2%)	47 (83.9%)	0	5,456 (77.2%)	13,988 (80.2%)	134 (92.4%)	1 (25.0%)	14,123 (80.3%)
2 Fills	377 (5.4%)	2 (3.6%)	0	379 (5.4%)	1,065 (6.1%)	2 (1.4%)	3 (75.0%)	1,070 (6.1%)
3 Fills	39 (0.6%)	3 (5.4%)	0	42 (0.6%)	152 (0.9%)	4 (2.8%)	0	156 (0.9%)
>3 Fills	2 (<0.1%)	0	0	2 (<0.1%)	8 (<0.1%)	0	0	8 (<0.1%)

Note: Closed system pharmacies refers to integrated healthcare systems that dispense TIRF medicines for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required by the TIRF REMS Access Program.

*Combined column reflects subjects who obtained prescriptions from both types of pharmacy systems.

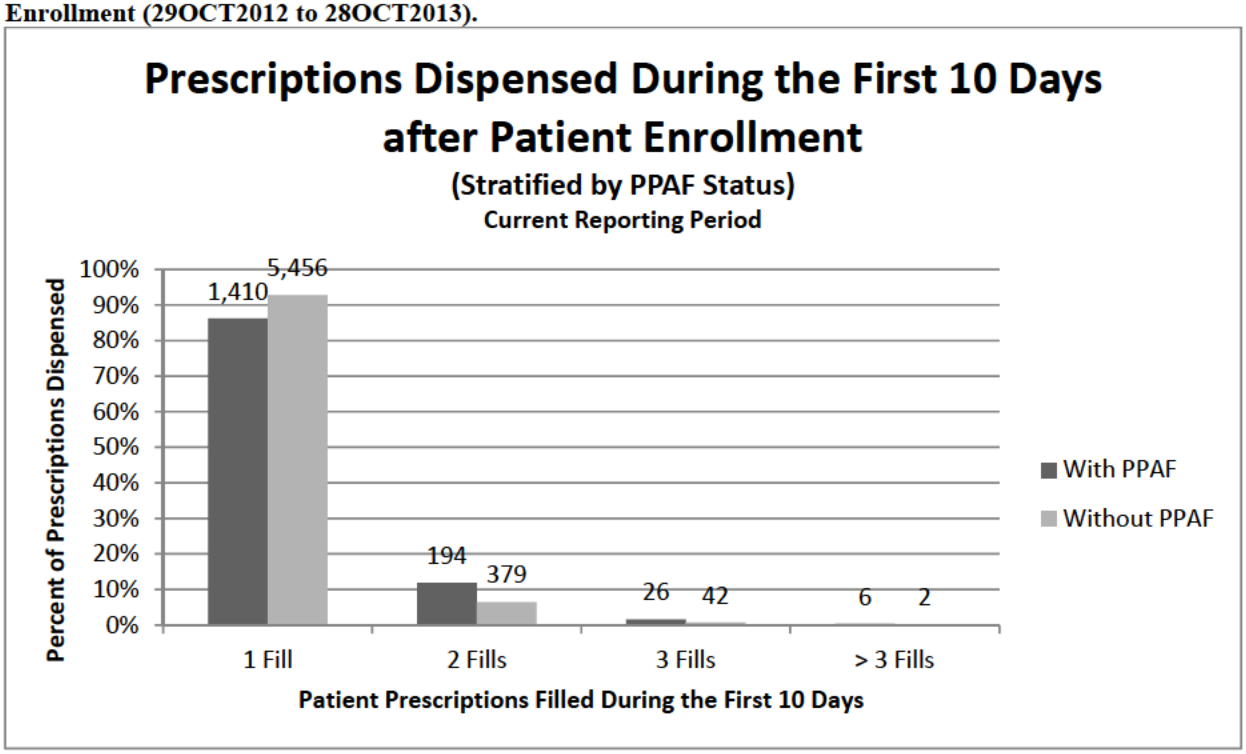
[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.

[b] Percentages are based on the total number of patients for the period. Sum of percentages may be greater than 100 due to patients receiving prescriptions with and without a PPAF during the grace period.

[c] A patient may receive up to 3 fills in the first 10 days after enrollment without a PPAF.

[d] A patient who have filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

Figure 2: Number of Patients Dispensed a Prescription During the First 10 Days After Patient Enrollment (29OCT2012 to 28OCT2013).



Prescriptions Dispensed Beyond 10 Days After Patient Enrollment

The TIRF REMS Access Program requires that each patient have a PPAF submitted to the TIRF REMS Access Program by their prescriber within 10 days of their passive enrollment in order to continue to receive a TIRF medicine. The table below shows the number of prescriptions dispensed beyond the first 10 days without a PPAF on file. From the inception of the TIRF REMS through the current reporting period, 242 patients have been dispensed at least 1 prescription beyond the first 10 days without a PPAF; 26 patients were in the current reporting period. However, as discussed below, corrective actions implemented in July 2013 have been effective at preventing any additional occurrences of this non-compliant activity.

Table 26: Prescriptions Dispensed Beyond the First 10 Days after Passive Patient Enrollment

	Current Reporting Period 29OCT2012 to 28OCT2013				Cumulative[a,b] 28DEC2011 to 28OCT2013			
Parameter	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined[b] Pharmacies N (%)**	**Filled at All Pharmacies N (%)**	**Filled at Non-Closed System Pharmacies N (%)**	**Filled at Closed System Pharmacies N (%)**	**Filled at Combined[b] Pharmacies N (%)**	**Filled at All Pharmacies N (%)**
Number of prescriptions dispensed to patients beyond the first 10 days after patient enrollment	12,927	87	61	13,075	146,740	531	1,311	148,582
Number of patients dispensed at least 1 prescription beyond the first 10 days after patient enrollment	2,972	24	7	3,003	11,187	79	98	11,364
Fills beyond the first 10 days Without PPAF[b]	25	0	1	26	230	0	12	242

[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.
[b] A patient who have filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

In the 12-month assessment report there was 1 patient who received more than 3 fills without a PPAF on file within a 10-day period. The TIRF REMS Access Program investigation of the root cause of this event continued into this reporting period. In this reporting period, there were an additional 3 patients who met the same criteria. The investigation included a review of these 4 cases and extended back to the beginning of the program (12 March 2012-28 October 2013), which identified another 3 cases. In each case the root cause was determined to be an insufficient system requirement for patient matching logic to cover changes to patient data elements during prescription processing. On 15 July 2013 the TIRF REMS Access Program finalized the required system enhancements to modify the patient matching in order to prevent patients receiving more than 3 prescriptions without a PPAF. Additionally, during the time when the system enhancement was being implemented, an additional data quality check was instituted to prevent future occurrences. As of 28 October 2013, all 7 patients have a PPAF on file. After the system enhancement was implemented no additional cases of more than 3 fills within the first 10-days in patients without a PPAF were identified, indicating that the corrective action was effective.

The investigation described above was also expanded to include patients who received any fills outside of the 10 days without a PPAF on file. The TIRF REMS Access Program investigation of the root cause of this event occurred in this reporting period. The investigation extended back to the beginning of the program identifying a total of 242 cases. In each case the root cause was determined to be the same as that identified for patients receiving more than 3 prescriptions within the first 10 days without a PPAF and the same corrective action was deemed appropriate. Multiple outreach attempts were conducted to the prescribers to obtain the PPAFs, and, as a result of the outreach, 182 patients now have a PPAF on file. Following the implementation of system enhancements on 15 July 2013 no additional cases of patients who received any fill outside of the 10 day grace period without a PPAF on file have been identified, indicating that the corrective action was effective.

5.3 Program Infrastructure and Performance [Metrics 19, 20, 21, 22, 23, 24]

5.3.1 Pharmacy Management Systems [Metric 19]

Table 27 summarizes the time it took enrolled outpatient pharmacies to configure their PMS to communicate with the REMS program. Of 675 outpatient pharmacies that attempted to configure a PMS, 95.6% successfully reconfigured their systems and 4.4% did not complete configuration of their PMS within the reporting period. It took a mean of 0.61 days to configure, with a minimum of 0.0001 days and a maximum of approximately 203.85 days. The 203.85 day outlier for the PMS configuration is an independent outpatient pharmacy that submitted their first PMS test transaction on 18 December 2012 and completed the last PMS test transaction on 10 July 2013 due to the pharmacy's decision to delay enrollment in the TIRF REMS Access Program.

Table 27: Configuration of Pharmacy Management System (PMS)

	Current Reporting Period 29OCT2012 to 28OCT2013	Cumulative 28DEC2011 to 28OCT2013
Parameter	**N (%)**	**N (%)**
Number of Outpatient Pharmacies Attempting to Configure PMS	675	3,483
Number of Outpatient Pharmacies with Incomplete Configuration of PMS[a]	30 (4.4%)	73 (2.1%)
Number of Outpatient Pharmacies Successfully Completing Configuration of PMS[b]	645 (95.6%)	3,410 (97.9%)
Time Required to Complete Configuration[c]		
Mean	0.6146	0.7843
Minimum	0.0001	0.0001
Maximum	203.85	203.85

[a] Defined as number of pharmacies with less than 3 dates of test transfers in the reporting period.

[b] Percentages are based on the total number (N) of pharmacies attempting to configure their PMS for the relevant period. For chain pharmacies, this refers to their corporate headquarters, not the number of individual store locations.

[c] Time measured in days from 1st transaction attempt to final transaction successful configuration.

5.3.2 Backup System for Prescription Validation [Metric 20]

During this reporting period there were no instances in which a backup system was used to validate a prescription due to pharmacy level problems, switch problems, or REMS database problems.

5.3.3 REMS Call Center [Metric 21a, b]

Table 28 below shows reasons for contacting the REMS Call Center by frequency (%). For presentation in the report, this table includes at least 80% of the total cumulative frequency. The most frequent reasons classified under the call reason were pharmacy: pharmacy claim rejection (16.0%) which indicated that the prescriber/patient was not enrolled, enrollment status inquiry (14.2%), PPAF status inquiry (12.8%), and general program questions (8.0%). The call reasons listed below in Table 28 represent 82.6% of calls to the Call Center for the current reporting period.

Table 28: Reasons and Frequency for Contacting the Call Center

Contact Reason	Current Reporting Period 29OCT2012 to 28OCT2013		
	Frequency	Percent[a]	Cumulative Percent
Pharmacy: Pharmacy Claim Rejection	3800	16.0%	16.0%
Enrollment Status Inquiry	3372	14.2%	30.2%
PPAF Status Inquiry	3031	12.8%	43.0%
General Program Questions	1904	8.0%	51.0%
Other/Miscellaneous	1669	7.0%	58.0%
Enrollment Follow Up	1643	6.9%	64.9%
PPAF Follow-up	1522	6.4%	71.3%
REMS Prescription Authorization Request	995	4.2%	75.5%
Enrollment Form	921	3.9%	79.4%
Relay Health Transfer-Tier 2 Support	769	3.2%	82.6%

[a] The total percentage presented in the table is 82.6% of all reasons for contacting the Call Center.

Problems or complaints related to patient access issues that were reported to the REMS Call Center for review by the TIRF REMS Access Program are summarized below. The cases described begin with cases reported in the 12-month assessment report but whose resolution occurred in this reporting period. In addition, new problems or complaints reported in this time period are described including their resolutions if attained. Any cases that were not resolved in this time period will be included in the 36-month assessment report.

Cases Reported in 12-month Assessment Report and Resolved in This Reporting Period

ID #1: Closed [Patient Access]
Issue: On 23 August 2012, a complaint letter was received from a prescriber regarding attestation language in the PPAF. The prescriber complained that the TIRF REMS requirement regarding opioid tolerance does not allow the physician to provide “best possible pain management to patients” and possibly requires ”over-prescribing of pain medication.”

Status reported in 12-month assessment report: A copy of the prescriber’s letter was submitted to FDA. This prescriber is currently enrolled in the TIRF REMS Access Program and has prescribed TIRF medicines. There was one paid claim recorded in the TIRF REMS Access Program for this prescriber.

Resolution: No new PPAF was received for this patient.

ID #2: Closed [Patient Access]
Issue: On 03 October 2012, a prescriber submitted a written complaint about PPAF attestation language. The TIRF REMS received a modified PPAF from the prescriber because the patient is not on around-the-clock opioid medication. The Call Center advised the prescriber that an altered PPAF could not be processed and requested the prescriber resubmit the PPAF. The same PPAF was re-submitted with letter of explanation from the patient's physician describing the patient's condition (i.e., not on ATC opioids). The PPAF was not processed because it was an altered PPAF and therefore did not meet the TIRF REMS requirements.

Status reported in 12-month assessment report: An email was sent to FDA requesting a teleconference to discuss requests to modify PPAFs.

Resolution: A new, unaltered PPAF was received and processed for this patient on 22 January 2013.

Cases Reported in This Reporting Period

ID #3: Closed
Issue: A chain outpatient pharmacy store advised the Call Center they would not process the patient's prescription until the pharmacy had a copy of the patient's PPAF. Pharmacist advised this was a corporate headquarters policy.

Resolution: TIRF REMS Access Program contacted a corporate headquarter representative. The headquarter representative contacted both pharmacists in the store (who are also the pharmacists in charge) and re-educated them on proper procedures. The patient has received medication.

ID #4: Closed
Issue: An outpatient pharmacy contacted the TIRF REMS Access Program Call Center to assist with enrolling them as an outpatient pharmacy when they were unable to complete the test transactions. They informed the Call Center that they do not have the ability to transmit claims electronically. The pharmacy (located in a hospital) allows their employees to fill prescriptions on a self-pay basis with themselves acting as the payer. TIRF REMS Access Program has confirmed they are a closed system with no outside access to third parties or other transmissions. There was one patient waiting for the TIRF medication.

Resolution: TRIG approved the pharmacy to enroll as a closed system pharmacy. Additional research was conducted to determine if the patient ultimately received drug. The pharmacy was contacted and the pharmacist indicated they referred this patient to a different pharmacy; however, it could not be confirmed if the patient received their TIRF medicine at the alternate pharmacy.

5.4 System Errors and Corrective Actions [Metric 22]

A brief summary of issues identified as system errors and their corrective actions is presented below. Additional system errors that met the definition of non-compliance are presented in Section 6.

System Error #1 Re-enrollment Reminders Were Not Sent to Stakeholders Whose Preferred Method was Email

Description: Re-Enrollment reminders were not being generated to prescribers and pharmacists where the preferred method of communication was e-mail as indicated on the TIRF REMS Access Program Enrollment Form. Stakeholders whose preferred method of communication was fax were not impacted. There were 6 stakeholders, all prescribers, who did not receive their re-enrollment reminder prior to deactivation.

Root Cause: The cause was determined to be insufficient coding logic and test case for this scenario.

Correction: Upon identification of this issue on 18 December 2013, the TIRF REMS Access Program generated a query to identify all potentially impacted stakeholders. Once identified, the TIRF REMS Access Program Call Center placed outbound calls to communicate re-enrollment notifications. The calls were completed on 21 January 2013. Any stakeholders unable to be reached via the outbound call were sent a fax notification which was completed on 20 February 2013. Until an automated solution to send re-enrollment notifications via email was implemented, daily reports were run to identify stakeholders who were scheduled to receive their re-enrollment reminders via email, and these stakeholders were informed about the need to re-enroll. The automated solution was implemented on 17 January 2013.

Resolution: At the end of this current reporting period, 2 of the 6 prescribers have re-enrolled, 1 is in the process of re-enrolling and the remaining prescribers are in a deactivated state.

System Error #2 Closed System Claim Transition

Description: On 28 December 2012, a message was received by the REMS Call Center stating that the NDC (National Drug Code) switch was inoperable when attempting to process claims through the closed system pharmacy claim adjudication system in support of the TIRF REMS closed system pharmacies. The issue was resolved on the same day, and four closed system claims were impacted.

Root Cause: The application requires a custom rule on the firewall to allow traffic via specific ports to the pharmacy network server. The custom rule was configured on the primary server firewall, but not the secondary server firewall. On 28 December 2012, transactions were routed through the secondary server due to network volume and these transactions failed because the firewall was not configured properly.

Correction: A rule was added to the second firewall to allow traffic to the closed system pharmacy claim adjudication system and the solution was implemented on 28 December 2012. Rule configuration changes were applied to both servers for future installations of this type on 23 January 2013.

Resolution: Four impacted claims were processed through the closed system pharmacy claim adjudication system on 31 December 2012.

System Error #3 TIRF REMS Access Program Hardware/Connectivity Issue

Description: On 08 November 2012 at 4:00pm, the TIRF REMS Access Program experienced a hardware issue which resulted in rerouting some traffic to a secondary router. The impact of the hardware issue caused 53 TIRF REMS transactions to reject back to the pharmacy with a "System Unavailable, Please Try Again Later" rejection. An analysis was performed by the TIRF REMS Access Program to determine the impact of the 53 unique transactions:

- 38 of the 53 transactions have been reprocessed by pharmacy and paid by the payer
- 11 of the 53 transactions were reprocessed and rejected by the payer/REMS
- 4 of the 53 transactions were voided by the pharmacy

Root Cause: Faulty network equipment

Correction: The TIRF REMS Access Program immediately rerouted some of the traffic to a secondary router to ensure transactions were processing as expected.

Resolution: The faulty network equipment was replaced on 11 November 2012.

System Error #4 REMS Transaction Bypassed REMS Edits

Description: A pharmacy at an academic medical center had an inbound communication line for transaction processing installed in late January. When installed, the REMS Pre- and Post-Edits were not enabled for this interface by the switch provider – therefore, 1 prescription was not submitted to the TIRF REMS Access Program.

Root Cause: When installed, the REMS Pre- and Post-Edits were not enabled for this interface.

Correction: REMS Pre- and Post-Edits were enabled for this circuit and a query was performed on all inbound circuits to confirm that the REMS Pre- and Post-Edits were properly set. All other circuits were properly set.

Resolution: Transaction was reversed from the third party adjudication. Each time a new circuit is installed, an automated email will be delivered to the TIRF REMS Access Program distribution indicating the status of REMS switches.

System Error #5 REMS Communication Line Migrated Without REMS Edits
Description: Between 28 May 2013 and 29 May 2013, the TIRF REMS Access Program performed scheduled network maintenance on outbound circuits. During this maintenance, there was a communication line that was migrated to complete the necessary updates required in the maintenance window. After the communication line was migrated, it was not updated to include TIRF REMS edits. There were 2 impacted transaction claims as a result: One transaction was rejected by the payer and not re-processed and 1 transaction was paid without REMS validation. The pharmacy was contacted on 30 May 2013 and requested that they reverse the transaction that had not been validated by the REMS and re-submit. The pharmacy completed this task on 30 May 2013 and the prescription passed all REMS edits.

Root cause: Configuration mismatch between primary and backup processes.

Correction: All configuration parameters leading to this particular event were reviewed and no other occurrences were found. The code element was removed which eliminated the need for a configuration setting to be used to invoke REMS services any longer. This was completed on 21 October 2013.

Resolution: The configuration error was corrected to execute the TIRF REMS Edits.

5.4.1 Lack of Enrolled Prescribers and/or Pharmacies for Patients [Metric 23]

During the current reporting period, the TIRF REMS Access Program received 1 report of difficulty accessing an enrolled prescriber. The prescriber reached out to the TIRF REMS Access Program Call Center on behalf of the patient who was moving and in need of a new enrolled TIRF medicines prescriber close to his/her new residence. The TRIF REMS Access Program CSR conducted a search of 6 zip codes which yielded 0 enrolled prescribers. The agent then broadened the search to include city and state and located an enrolled prescriber. No reports of inadvertent enrollment deactivations were identified.

5.4.2 Delays after Prescription Denial [Metric 24]

The prescription conversion time or length of time delay is defined as the length of time between the initial reject on a claim to when it successfully passes all the REMS business rules/edits and is sent to the payer of adjudication.

For the assessment period, 29 October 2012 through 28 October 2013:

- The mean prescription conversion time was 2 days, 2.358 hours.
- The median prescription conversion time was 0 days, 0.227 hours.
- The minimum prescription conversion was 0 days, 0.001 hours.
- The maximum prescription conversion time was 519 days, 22.007 hours.

There was one outlier of 519 days and 22.007 hours that impacted the maximum prescription conversion time. On 11 April 2012, one independent outpatient pharmacy transmitted a TIRF REMS prescription that did not pass the REMS edits. This transaction was rejected for Prescriber Not Enrolled. On 13 September 2013 (519 days later), the pharmacy resubmitted the claim, the transaction passed the REMS edits but was reversed on the same day.

5.5 Unintended System Interruptions [Metrics 25, 26, 27, 28]

5.5.1 Inadvertent Enrollment Deactivations [Metric 25]

During this reporting period there were no inadvertent prescriber deactivations.

5.5.2 Reports of False Positives [Metric 26]

During this reporting period, there were no reports of a false positive incident.

5.5.3 Failure of Re-enrollment Notifications [Metric 27]

Re-enrollment notifications were sent to a total of 1,172 prescribers via fax and 1,424 prescribers via e-mail this reporting period. Of these, 1,086 prescribers successfully received a notification for re-enrollment via fax and 1,406 prescribers via e-mail. By the end of the reporting period, there were a total of 87 unique prescriber re-enrollment notifications that were unable to be delivered via fax and 18 unique prescriber notifications unable to be delivered via e-mail despite multiple attempts. In the event that the prescriber is unable to be contacted via fax, the TIRF REMS Access Program places an outbound call in an attempt to obtain the correct contact information. If updated information is obtained, the re-enrollment notification is re-sent.

5.5.4 Reports of False Negatives [Metric 28]

During the reporting period, there were no reports of a false negative where all entities were enrolled but the system generated a rejection notice.

5.5.5 Duplicate Stakeholder Records

In response to the 12-month assessment report, FDA posed a question concerning identification and handling of duplicate reports. As a consequence FDA asked for 3 new metrics which are listed below.

3.e.i.	The number of duplicate prescribers, patients, and pharmacies identified in the system.
3.e.ii	Why the duplications were not originally detected.
3.e.iii.	The corrective actions taken to assure minimization of future duplicative data entries

The investigation of duplicate reports identified that records that were classified as “obsolete” had been included in the stakeholder counts reported in the previous assessment reports.

Programming has been updated to ensure that "obsolete" records are excluded from this and future reports.

Duplicate Prescriber and Pharmacy Records

The system does not allow duplicate records to be created for prescribers and pharmacists due to the unique identifiers required for enrollment (i.e., DEA, NPI, NCPDP).

Duplicate Patient Records

Patient records are created by the processing of a patient's first paid TIRF prescription (i.e., passive patient enrollment), or by the receipt of a Patient-Prescriber Agreement Form (PPAF). As a result, the TIRF REMS Access Program has two systematic methods utilized to handle patient duplicates.

First, the TIRF REMS Access program systemically identifies and rectifies duplicate records utilizing patient matching logic consisting of key patient identifiers (i.e. Date of Birth, First Name, Last Name, and Zip Code). This occurs as part of the normal course of business when passive patient enrollments and PPAFs are processed; therefore duplicate patient records are not created.

Second, the TIRF REMS Access Program systematically identifies potential patient duplicates, which generates a daily report to the TIRF REMS Access Program Call Center to ultimately determine if the record is a valid duplicate. Valid duplicates identified by the TIRF REMS Access Program Call Center are merged into one patient record. A total of 733 duplicate patient records were identified and merged during the 24-month assessment period.

Because the system does not allow duplicate records to be created for prescribers and pharmacists due to the unique identifiers required for enrollment TRIG questions the utility of this metric for stakeholders. However, reporting on the number of merged patient records is a metric the TRIG would like to discuss with FDA in January 2014 as a follow-up to the proposed changes to the assessment plan dated 19 September 2013.

5.6 Audits

No stakeholder audits were conducted during the current reporting period.

6 TIRF REMS ACCESS PROGRAM NON-COMPLIANCE

During the current reporting period, instances of potential stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. A summary of the non-compliance activity is presented in Table 29.

Table 29 Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period: 29 October 2012 to 28 October 2013

Stakeholder	Non-Compliance Activity	Non-Compliant Reason (categorized as reported by the stakeholder)	Current Reporting Period	
			No. of events	No. of stakeholders
Non-Closed System Pharmacy	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)	Altered RX details for a REMS authorization	2	No. w/1 rpt: 2
	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF pharmacy management system that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Received reject but dispensed drug	22	No. w/1 rpt: 18 No. w/2 rpt: 2
		Not aware of requirement to process cash claims	3	No. w/1 rpt: 3
		Not aware of cash claim and received reject but dispensed drug	4	No. w/1 rpt: 4
		Total	**31**	**29**
Closed System Pharmacy	Dispensing prescriptions outside of the closed system authorization process.	Dispensed drug without obtaining an authorization	2	No. w/1 rpt: 2
		Total	**2**	**2**
Prescriber	Prescriber failure to submit completed PPAFs in a timely manner (5 or more enrolled patients without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date).	No reason provided*	8	No. w/1rpt: 8
		Not aware of PPAF requirement	84	No. w/1 rpt: 80 No. w/2 rpt: 2
		Total	**92**	**90**

*No reason provided by stakeholder after multiple outreach attempts.

The following tables (Table 30 and Table 31) list resolved and pending potential reports of non-compliance, respectively.

Table 30 Follow-up From the 12 Month Assessment Report

Report No.[1]	Report Description	Report Status	Mitigating Action
13	Closed System Pharmacy: The TIRF REMS Access Program administrator identified that the program had not received any prescription authorizations from the Veteran's Administration (VA) since the closed system pharmacy effective day of 01 July 2012. Following multiple outreach attempts to the VA, the program received contact from the VA Authorized Representative on November 15th confirming that there had been TIRF prescriptions dispensed without obtaining an authorization to dispense from the Closed System Program. (CAPA 341)	Closed	The VA conducted a thorough search across the entire VA system and confirmed that there were TIRF prescriptions dispensed between 01 July 2012 and 30 November 2012. As stated in the communication sent to FDA on January 25, 2013, there were a total of 85 dispenses from 15 closed system outpatient VA pharmacies for 19 unique patients during this time period. Of the 85 dispense records, 28 dispenses met the safe use conditions and would have received an Rx Authorization if the program was contacted correctly prior to dispense. The remaining 57 dispense records would not have received Rx Authorizations for the following reasons: prescriber not enrolled (38); pharmacy not enrolled (8); PPAF not on file (6); incomplete TIRF medicine NDC (5). Stakeholders affected by the 57 records that did not meet all REMS requirements included: 13 unique prescribers; 3 unique pharmacies; 2 unique patients requiring a PPAF; 2 unique patients with an incomplete NDC on the dispense record. The VA was re-educated on the REMS requirements and issued a formal Notice for Non-Compliance. As of 31 October 2013, 3 additional prescribers have enrolled in the TIRF REMS Access Program bringing the total number of unique stakeholders associated with the VA that are enrolled in the TIRF REMS Access Program to 9. Additionally the VA had a total of 86 prescription authorizations issued as of 31 October 2013.

Table 31 Reports in the Current Reporting Period: 29 October 2012 to 28 October 2013

14	ID# 29 (Case #11793909) On 06 November 2012, a prescriber was contacted to request a PPAF for a patient who did not have one on file at least 10 days after enrollment (transaction was submitted on October 19). The prescriber claimed the patient in question was not a patient of his/her practice and a similar scenario with the pharmacy and prescriber had occurred previously in March 2012. The TIRF REMS Access program non-compliance team contacted the pharmacy associated with the REMS authorized prescription for additional information. It was discovered that when an Outpatient Chain Pharmacy Store processed this prescription on 16 March 2012, the pharmacy received a rejection from the TIRF REMS Access Program for the reason "prescriber not enrolled." The pharmacy then re-processed the prescription, but used another prescriber's DEA number. This time, the transaction was authorized by the REMS. The pharmacy was contacted on 11 November 2012, re-educated on the TIRF REMS Access Program requirements, and sent a formal Warning for Non-Compliance letter. The pharmacy requested that the TIRF REMS Access Program also directly contact the pharmacy's chain headquarters to resolve this issue and address any further inquiry.	Closed	After re-education, the TIRF REMS Access Program worked with the pharmacy chain headquarters to develop a corrective action plan. An acceptable corrective action plan stating that the chain pharmacy store would dispense TIRF medications only after submitting a claim properly and receiving approval for the claim was received on 04 March 2013 and approved on 08 March 2013 by the NCRT. The chain pharmacy store's activity was monitored through 19 July 2013, and all activity observed during this period appeared in compliance with program requirements. This is the first confirmed report of non-compliance for this chain pharmacy store to date. The transaction submitted on 19 October 2012 for the patient without a PPAF on file was reversed on October 19, 2012. The original prescriber who wrote the prescription was identified during the investigation and subsequently enrolled in the TIRF REMS Access Program; a PPAF was submitted for the patient.
15	ID# 54 (Case #12146501) On 25 October 2012, the TIRF REMS Access Program contacted a prescriber to obtain a PPAF for a patient who was at least 10 days past enrollment without a PPAF on file. The prescriber reported that he routinely does not submit PPAFs because he only writes one prescription for TIRF medicines for each of his patients. At the time of investigation, 18 patients enrolled by this prescriber did not have a PPAF on file.	Closed	On 12 November 2012, the prescriber was re-educated on the TIRF REMS Access Program requirements and issued a formal Notice for Non-Compliance. The prescriber was unable to provide any PPAFs for these patients. Subsequent to re-education, the prescriber enrolled an additional patient on 19 December 2012 without submitting a PPAF. The prescriber was contacted on 11 January 2013, re-educated again on the requirement to submit PPAFs for enrolled patients, and issued a formal Warning for Non-Compliance letter since the second non-compliant event occurred within 60 days from the initial. The prescriber submitted a corrective action plan stating the prescriber would complete a PPAF at the time when the prescription is written. This corrective

Table 31 Reports in the Current Reporting Period: 29 October 2012 to 28 October 2013

			action plan was approved by the NCRT on 23 January 2013. The prescriber activity was monitored through 07 March 2013; no additional patients were enrolled during this period. As of the close of the reporting period, no PPAFs were received for the 19 (total) patients and no additional prescriptions were submitted for these patients. Since closing the non-compliance cases, the prescriber has not enrolled any additional patients in TIRF REMS Access Program.
16	ID# 73 (Case #14089142) During regular compliance monitoring, a prescriber was identified as not submitting PPAFs for 36 patients who were at least 10 days past enrollment. The prescriber was contacted on 07 March 2013, re-educated on the TIRF REMS Access Program requirements, and issued a formal Notice for Non-Compliance letter. The prescriber submitted PPAFs for 34 of the 36 patients (2 patients were identified as not continuing therapy). The REMS activity for this prescriber was monitored through 07 May 2013 with no additional findings. On 27 June 2013, the prescriber was again identified as not submitting PPAFs for an additional 16 patients who were at least 10 days past enrollment.	Closed	The prescriber was contacted on 11 July 2013, re-educated, and issued a second formal Notice for Non-Compliance letter since this second event was greater than 60 days from the initial noncompliant event. The prescriber provided PPAFs for 3 of these 16 patients identified on 27 June 2013. As of the close of the reporting period, PPAF's have not been received for any of the 15 remaining patients from the non-compliance cases above. Fourteen of the patients have not submitted an additional prescription for a TIRF medicine; 1 of the 15 patients had a rejected claim due to no PPAF on file. Since re-education and closing of the second non-compliance case, the prescriber has no new patients without a PPAF on file outside of the 10-day window.
17	ID# 89 (Case #14088956) During regular compliance monitoring, a prescriber was identified as not submitting PPAFs for 62 patients who were at least 10 days past enrollment. The prescriber was contacted on 14 March 2013, re-educated on the TIRF REMS Access Program requirements, and issued a formal Notice for Non-Compliance letter. The prescriber submitted 27 of the 62	Closed	The prescriber was contacted on 26 June 2013, re-educated, and requested to provide PPAFs for these patients. None were provided. TIRF REMS Access Program supported the prescriber over several weeks to maintain compliance with program requirements. During this time, the prescriber enrolled an additional 27 patients and submitted PPAFs for all of these patients. A second formal Notice for Non-Compliance letter was

Table 31 Reports in the Current Reporting Period: 29 October 2012 to 28 October 2013

	outstanding PPAFs and confirmed that the remaining 35 patients were identified as not continuing therapy. On 19 June 2013, the prescriber was again identified for not submitting PPAFs for an additional 18 patients.		issued on 12 August 2013 since the second event was greater than 60 days from the initial noncompliant event. As of the close of the reporting period, PPAF's have not been received for any of the 53 outstanding patients from the non-compliance cases above. Three of the 53 patients have attempted to have a prescription filled for a TIRF medicine outside of the 10-day window without a completed PPAF on file, however the REMS rejected these prescription attempts due to no PPAF on file. For the remaining 50 patients, no prescriptions have been submitted. Since re-education and closing of the second non-compliance case, the prescriber has no new patients without PPAFs on file outside of the 10-day window.
18	ID# 96 (Case #14089163) During regular compliance monitoring, a prescriber was identified as not submitting PPAFs for 11 patients who were at least 10 days past enrollment. The prescriber was contacted on 09 April 2013, re-educated on the TIRF REMS Access Program requirements, and issued a formal Notice for Non-Compliance letter. PPAFs were received for all 11 patients. On 19 June 2013, the prescriber was again identified as not submitting PPAFs for an additional 8 patients who were at least 10 days past enrollment.	Closed	The prescriber was contacted in July 2013, re-educated, and requested to provide PPAFs for these patients. The prescriber was able to provide PPAFs for 3 of these patients. TIRF REMS Access Program supported the prescriber over several weeks to maintain compliance with program requirements. During this time, one additional patient was enrolled by the prescriber and a PPAF was submitted. A second formal Notice for Non-Compliance letter was issued on 17 August 2013 since this second event was greater than 60 days from the initial noncompliant event. As of the close of the reporting period, PPAFs were received for 3 of the patients. PPAFs were not received for 2 of the 5 patients. These 2 patients have attempted to have a prescription filled for a TIRF medicine; however the REMS rejected these prescription attempts due to no PPAF on file. Since re-education and closing of the second non-compliance case, the prescriber has 0 new patients without PPAFs on file outside of the 10-day window.
19	ID# 102 (Case #15529127) On 12 March 2013, a prescriber was contacted to request	Closed	The prescriber was contacted on 09 September 2013, re-educated, and requested to provide PPAFs for these patients. The prescriber

Table 31 Reports in the Current Reporting Period: 29 October 2012 to 28 October 2013

	PPAFs for 18 patients who did not have one on file at least 10 days after enrollment. The prescriber was re-educated on the TIRF REMS Access Program requirements, and issued a formal Notice for Non-Compliance letter. PPAFs were received for 17 of the 18 patients. On 02 September 2013, the prescriber was again identified as not submitting PPAFs for an additional 7 patients who were at least 10 days past enrollment.		was able to provide PPAFs for all 7 of these patients. A second formal Notice for Non-Compliance letter was issued on 29 September 2013 since this second event was greater than 60 days from the initial noncompliant event. As of the close of the reporting period, a PPAF has not been received for one patient. Since closing the second non-compliance case, the prescriber has 3 new patients without PPAFs on file, all outside of the 10-day window. These 3 patients have not attempted to fill any additional TIRF medicine prescription. A new suspected non-compliance case will be opened if the number of patients without a PPAF outside of the 10-day window reaches the threshold of 5.
20	ID# 121 (Case#) On 09 September 2013, a prescriber was contacted to request PPAFs for 5 patients who did not have one on file at least 10 days after enrollment. The prescriber provided PPAFs for 2 of the patients, but stated that 3 of the patients in question were not from his/her practice.	Open	On 10 September 2013, the TIRF REMS Access Program contacted the independent pharmacy associated with the REMS authorized prescriptions for additional information. The pharmacy was unwilling to provide any information on these 3 patients and disconnected the call. All transactions from the pharmacy were reviewed by the NCRT. Seven claims involving 6 patients (including the 3 patients noted above) were identified where the patient's name was reversed (first name entered as last name, last name entered as first name) after the pharmacy received a rejection from the TIRF REMS Access Program for the reason "no PPAF on file." The pharmacist in charge was contacted on 04 October 2013 and the pharmacist in charge explained that these claims were from electronic prescriptions and processed with the information as it was provided (i.e., names were switched on original prescription). Based on this evidence, the pharmacy was issued a formal Warning for Non-Compliance letter. Additionally, the pharmacy was required to provide a corrective action plan that was approved by the NCRT on 06 November 2013 stating that all pharmacy staff

Table 31 Reports in the Current Reporting Period: 29 October 2012 to 28 October 2013

			members have been trained on the program and have been educated on the importance of inputting correct patient data prior to transmitting pharmacy claims. Additionally all TIRF REMS claims will be checked and verified by a pharmacist. Additional monitoring will also occur for a minimum of 1 month to ensure this pharmacy does not continue this non-compliant activity.
21	ID# 127 (Case# 15791475) On 28 January 2013, a prescriber was contacted to request PPAFs for 13 patients who did not have one on file at least 10 days after enrollment. The prescriber was re-educated on the TIRF REMS Access Program requirements, and issued a formal Notice for Non-Compliance letter. The prescriber submitted all 13 outstanding PPAFs. On 17 September 2013, the prescriber was again identified for not submitting PPAFs for an additional 11 patients.	Open	The TIRF REMS Access Program made 3 attempts to contact the prescriber, but was advised by the prescriber's office staff that the prescriber "refused to come to the phone regarding PPAF calls from TIRF REMS Access." By 21 October 2013, only 1 of the 11 outstanding PPAFs were received, and 3 additional patients were identified who did not have a PPAF on file at least 10 days after enrollment. As of the close of the reporting period, PPAFs have not been obtained for any of the 13 patients. Seven new patients have been enrolled without a PPAF on file outside of the 10-day window. To date, the prescriber has a total of 20 patients enrolled without a PPAF. A warning letter requesting a corrective action plan was issued to the prescriber 05 November 2013.

Table 31 Reports in the Current Reporting Period: 29 October 2012 to 28 October 2013

22	ID# 128 (Case# 11744815) On 11 June 2012, the TIRF REMS Access Program contacted a prescriber to obtain a PPAF for a patient who was enrolled in the program on 08 June 2012. The prescriber's office staff reported the patient in question died in (b) (6). The pharmacy that processed the prescription confirmed the date of the prescription as 07 June 2012, and verified the pharmacy processed the prescription on 08 June 2012. The TIRF REMS Access Program confirmed that the pharmacy reversed the claim indicating that no TIRF medicine was dispensed.	Closed	The prescriber was contacted to confirm if the prescription was written after the patient's death. The prescriber requested, and was provided, a copy of the prescription in question. The prescriber contacted the TIRF REMS Access Program after reviewing the prescription and reported the office has two patients with the same name, one who died and one who was still living, and cited an office error as the source of confusion. Based on this evidence, this case of suspected non-compliance was closed as not a non-compliant event and the details of the case were shared with the sponsor of the product for appropriate follow-up.

[1] For tracking purposes across TIRF REMS Access Program assessment reports, noncompliance reports are numbered consecutively and continuously from the first TIRF REMS Access Program Assessment Report.

7 SAFETY SURVEILLANCE

7.1 Adverse Events

The following Quarterly Analysis report was produced from the cumulative 2012 Q4 release of the FDA Adverse Event Reporting System (FAERS) database which was made publicly available by the FDA in early October 2013. This Analysis Report focuses on the latest 2 quarters of the AERS data, Q3 and Q4 2012, which are new since the last Quarterly Analysis report was delivered using the Q2 2012 AERS data. As AERS releases are cumulative, the data for both quarters are contained in the most recent Q4 2012 release.

The FAERS 2012 Q4 database is comprised of 4,073,790 cumulative case reports, including 232,989 new reports and 115,427 reports from the Q3 2012 quarterly release. Of the cumulative case reports included in this release, seventy-one (71) cases reference a (TIRF medicine covered by this REMS, with an event date on or after December 28, 2011. Fifty-three (53) of these 71 TIRF product case reports with an event date after December 28, 2011 also specify United States as the Country of Origin and are included in the analysis results described below. Sixteen (16) of these 53 domestic cases are new since the last TRIG Surveillance report was produced using the Q2 2012 release of the AERS data for inclusion in the 12 Month TIRF REMS Assessment Report.

Thirty-four (34) of the 53 domestic cases include at least one of the TRIG MedDRA Preferred Terms of Interest and are included in the analysis. Eight (8) of these 34 cases with a TRIG MedDRA Preferred Terms of Interest are new since the last TRIG Surveillance Report was produced using the Q2 2012 release of the AERS data for inclusion in the 12 Month TIRF REMS Assessment Report.

These MedDRA Preferred Terms of Interest are grouped into the following broad Categories of Interest (TRIG Categories) for aggregate reporting:

- Death
- Overdose (fatal and non-fatal)
- Misuse, abuse, addiction, and diversion
- Inappropriate prescribing
- Medication errors
- Accidental exposure/ingestion

In addition, 1 of the 53 cases that specifies at least one Preferred Term from the MedDRA SMQ (Broad) *Acute Central Respiratory Depression, (Preferred Terms are located in Appendix*

FAERS Safety Surveillance Report) is included in this analysis as it contains a possible symptom related to the events included in the TRIG Categories above. None of the individual Preferred Terms from this SMQ is a TRIG Preferred Term of interest, but counts of reports listing any PT from this SMQ will be summarized into an aggregate count for the entire SMQ and reported separately.

The following table summarizes the adverse event Terms and Categories of Interest that were reported in the cases for TIRF products that met the selection criteria for this analysis. A total of 46 PTs of Interest were reported across 34 cumulative case reports that contained a PT of Interest. Ten Preferred Terms were included in the 8 new cases that were submitted since the last AERS Surveillance analysis. Cumulatively, the most commonly reported Term is "Off label use" (23 cumulative / 5 new) followed by "Drug prescribing error" (8 cumulative / 1 new). Three of the 8 new cases contain the Preferred Term "Death" as one of the reported adverse events, representing 30% of all Preferred Terms of Interest reported on new cases. Tallies of the reported PTs and categories are summarized in the table below:

Table 31 Count of Reported Events of Interest Grouped by TRIG Category : Q3-Q4 2012

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	**%**	**N**	**%**
Overdose	**0**	0.0%	**0**	0.0%
Accidental overdose	0	0.0%	0	0.0%
Intentional overdose	0	0.0%	0	0.0%
Overdose	0	0.0%	0	0.0%
Death	**3**	30.0%	**3**	6.5%
Accidental death	0	0.0%	0	0.0%
Agonal death struggle	0	0.0%	0	0.0%
Apparent death	0	0.0%	0	0.0%
Brain death	0	0.0%	0	0.0%
Cardiac arrest	0	0.0%	0	0.0%
Cardiac death	0	0.0%	0	0.0%
Cardio-respiratory arrest	0	0.0%	0	0.0%
Death	3	30.0%	3	6.5%
Death neonatal	0	0.0%	0	0.0%
Death of companion	0	0.0%	0	0.0%
Death of relative	0	0.0%	0	0.0%
Respiratory arrest	0	0.0%	0	0.0%

Table 31 Count of Reported Events of Interest Grouped by TRIG Category :
Q3-Q4 2012

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	%	N	%
Sudden cardiac death	0	0.0%	0	0.0%
Sudden death	0	0.0%	0	0.0%
Sudden unexplained death in epilepsy	0	0.0%	0	0.0%
Misuse	0	0.0%	**0**	0.0%
Intentional Drug Misuse	0	0.0%	0	0.0%
Medication overuse headache	0	0.0%	0	0.0%
Drug abuse dependence and withdrawal SMQ	*1*		7	
Abuse	0	0.0%	**0**	0.0%
Drug abuse	0	0.0%	0	0.0%
Drug abuser	0	0.0%	0	0.0%
Ex-drug abuser	0	0.0%	0	0.0%
Substance abuse	0	0.0%	0	0.0%
Substance abuser	0	0.0%	0	0.0%
Substance-induced mood disorder	0	0.0%	0	0.0%
Substance-induced psychotic disorder	0	0.0%	0	0.0%
Drug abuse dependence and withdrawal SMQ	*1*		7	
Inappropriate Prescribing	5	50.0%	23	50.0%
Drug administered at inappropriate site	0	0.0%	0	0.0%
Drug administered to patient of inappropriate age	0	0.0%	0	0.0%
Drug administration monitoring procedure incorrectly performed	0	0.0%	0	0.0%
Drug administration monitoring procedure not performed	0	0.0%	0	0.0%
Inappropriate schedule of drug administration	0	0.0%	0	0.0%
Off label use	5	50.0%	23	50.0%
Medication Error	1	10.0%	13	28.3%
Accidental drug intake by child	0	0.0%	0	0.0%
Counterfeit drug administered	0	0.0%	0	0.0%
Drug administered to patient of inappropriate age	0	0.0%	0	0.0%
Drug administration error	0	0.0%	1	2.2%
Drug dispensing error	0	0.0%	1	2.2%
Drug dose omission	0	0.0%	1	2.2%

Table 31 Count of Reported Events of Interest Grouped by TRIG Category : Q3-Q4 2012

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	%	N	%
Drug label confusion	0	0.0%	0	0.0%
Drug name confusion	0	0.0%	0	0.0%
Drug prescribing error	1	10.0%	8	17.4%
Expired drug administered	0	0.0%	1	2.2%
Inappropriate schedule of drug administration	0	0.0%	0	0.0%
Incorrect dose administered	0	0.0%	0	0.0%
Incorrect dosage administered	0	0.0%	0	0.0%
Incorrect drug administration duration	0	0.0%	0	0.0%
Incorrect drug administration rate	0	0.0%	0	0.0%
Incorrect drug dosage form administered	0	0.0%	0	0.0%
Incorrect route of drug administration	0	0.0%	0	0.0%
Incorrect storage of drug	0	0.0%	0	0.0%
Intercepted drug dispensing error	0	0.0%	0	0.0%
Intercepted drug prescribing error	0	0.0%	0	0.0%
Intercepted medication error	0	0.0%	0	0.0%
Labeled drug-disease interaction medication error	0	0.0%	0	0.0%
Labeled drug-drug interaction medication error	0	0.0%	0	0.0%
Medication error	0	0.0%	0	0.0%
Multiple use of single-use product	0	0.0%	0	0.0%
Poor quality drug administered	0	0.0%	0	0.0%
Prescribed overdose	0	0.0%	0	0.0%
Prescribed underdose	0	0.0%	0	0.0%
Therapy naïve	0	0.0%	0	0.0%
Underdose	0	0.0%	0	0.0%
Wrong drug administered	0	0.0%	0	0.0%
Wrong technique in drug usage process	0	0.0%	1	2.2%
Accidental Exposure	0	0.0%	**0**	0.0%
Accidental drug intake by child	0	0.0%	0	0.0%
Accidental exposure to product	0	0.0%	0	0.0%
Accidental overdose	0	0.0%	0	0.0%

Table 31 Count of Reported Events of Interest Grouped by TRIG Category : Q3-Q4 2012

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	%	N	%
Accidental poisoning	0	0.0%	0	0.0%
Toxicity to various agents	0	0.0%	0	0.0%
Dependence	1	10.0%	7	15.2%
Dependence	0	0.0%	0	0.0%
Drug dependence	1	10.0%	1	2.2%
Drug dependence, antepartum	0	0.0%	0	0.0%
Drug dependence, postpartum	0	0.0%	0	0.0%
Drug Withdrawal Syndrome	0	0.0%	3	6.5%
Polysubstance dependence	0	0.0%	0	0.0%
Withdrawal syndrome	0	0.0%	3	6.5%
Drug Diversion	5	50.0%	23	50.0%
Drug diversion	0	0.0%	0	0.0%
Off label use	5	50.0%	23	50.0%
Respiratory Depression	0	N/A	1	N/A
Acute central respiratory depression SMQ	*0*		1	

A data mining (disproportionality) analysis was also performed on the selected AERS cases, using the entire AERS database as the background denominator. Relatively robust signals of disproportionate reporting were generated for the PTs of Interest: "Off label Use" and "Drug prescribing error". A weaker signal was generated for the Preferred Term of Interest "Drug withdrawal syndrome", which is a known adverse event for TIRF medicines. When analyzed according to TRIG Categories of Interest, relatively robust signals were also generated for "Inappropriate use", "Drug diversion", "Medication error", and "Drug dependence". When examined by MedDRA SMQ, the SMQ "Drug abuse, dependence and withdrawal" generated a weaker signal of disproportionate reporting. These results are similar to those seen in the last quarterly analysis, and no additional signals have been identified.

7.2 American Association of Poison Control Centers (AAPCC)

The AAPCC database is monitored to identify reports of misuse, abuse, and overdose. The AAPCC database includes all 57 poison centers in the US. Reports were requested from AAPCC on calls related to the aggregated data for the class of immediate-release transmucosal fentanyls (no manufacturer names or brand names are provided). The search also included

reports of unknown manufacturer oral immediate-release fentanyl products, and "unknown fentanyls" with oral and/or inhalation/nasal route(s) of exposure. AAPCC listings of reports for TIRF medicines and unknown fentanyl are presented in Appendix 12.2.

In the current reporting period (29 October 2012 to 28 October 2013), the AAPCC received 17 reports of exposure to known oral fentanyl immediate-release medicines. The 17 cases had medical outcomes of 2 deaths, 5 major effects, 4 moderate effects, 2 minor effects, 1 no follow-up minimal toxicity, and 1 no follow-up potentially toxic. “Effect” is defined as sign, symptom, or laboratory abnormality and described as minor, moderate, major, or death (See Appendix 12.2 for effect definitions).

Twenty cases of exposure to unknown fentanyl were reported to the AAPCC during the current reporting period. The cases had medical outcomes of 2 deaths (indirect reports), 3 major effects, 8 moderate effects, 3 minor effects, 3 unable to follow/judged as potentially toxic exposure, and 1 no effect. Both deaths were classified as intentional abuse. Four reports were characterized as intentional suspected suicide, all of these patients survived (Appendix 12.2).

Of note, 3 cases included in the AAPCC data were classified as exposures to a TRIF medicine, although the only fentanyl noted in the case was for a patch. When questioned about this report, an AAPCC representative provided this response:

> *“All of the fields are manually coded by the SPI based on self-report information by the caller. I confirmed that all three of these cases are coded specifically to one of the TIRF products’ unique 7-digit Poisindex product identifiers. SPIs make every attempt to code to the exact product involved – they will ask the caller to read off the box/bottle, read the imprint code, etc. to try to determine the exact product, strength and manufacturer. The SPIs then look up the provided information in Poisindex and select the entry that matches the information provided by the caller. When the SPI selects the product involved, the case in their local database is automatically populated with that product’s unique 7-digit Poisindex product identifier.*
>
> *I can’t speak with certainty about what was said on the calls or why the SPIs chose to code the cases as they did, but I will say that Poisindex lists the formulation for the 3 TIRF products in question as “Mucous membrane lozenge/troche”. However, the NPDS Formulation variable does not list this as one of the options for the SPIs to select. There may be confusion on the SPIs part regarding which Formulation option to select in the absence of a “Mucous membrane lozenge/troche” option.”*

Detailed information on the reports of death will not be available from the AAPCC until December 2014.

The following tables (Tables 20-26) include reports for exposures to TIRF medicines received between 29 October 2012 and 28 October 2013. The tables do not include reports for unknown fentanyl products.

Human Exposure Cases: Site of Call/Site of Exposure

As shown in Table 32 for the current reporting period, of the 17 human exposures associated with TIRF medicines reported. Of the 17 most of the exposures (n=13) occurred in the patients' own residences. Beyond residences, 1 exposure occurred in a health care facility, 1 in a public area and 2 exposure sites were unknown. Most of the reports originated from a health care facility (n=14).

Table 32: Site of Call and Site of Exposure, Human Exposure Cases Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Site	Site of Exposure Case Count	Site of Caller Case Count
Health Care Facility	1	14
Other	0	1
Own Residence	13	2
Public Area	1	0
Unknown	2	0
Total	**17**	**17**

Human Exposure Cases: Age and Gender Distribution

The age and gender distribution of human exposures associated with TIRF medicines is outlined in Table 33. There was one pediatric/adolescent exposure in a male in the age group 3 to 19 (age 16). Another 16 exposures were reported in adults 20 years of age or older, the majority of which were in the 20-29 age group (35.3%).

Table 33: Age and Gender Distribution of Human Exposures Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Age (yr)	Male N (%)	Female N (%)	Unknown N (%)	Total N (%)
1	0	0	0	0
2	0	0	0	0
3-19	1 (10.0%)	0	0	1 (5.9%)
20-29	4 (40.0%)	2 (28.6%)	0	6 (35.3%)

Table 33: Age and Gender Distribution of Human Exposures Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Age (yr)	Male N (%)	Female N (%)	Unknown N (%)	Total N (%)
30-39	3 (30.0%)	0	0	3 (17.6%)
40-49	1 (10.0%)	2 (28.6%)	0	3 (17.6%)
50-59	1 (10.0%)	1 (14.3%)	0	2 (11.8%)
60-69	0	0	0	0
70-79	0	1 (14.3%)	0	1 (5.9%)
Unknown adult (>=20 yrs)	0	1 (14.3%)	0	1 (5.9%)
Total	**10 (58.8%)**	**7 (41.2%)**	**0**	**17 (100.0%)**

All fatalities – All Ages and Gender

There were 2 fatalities reported in the AAPCC data associated with known exposures to TIRF medicines: 1 female in the 50 to 59 age group and 1 female in the 70 to 79 age group (AAPCC Database Table 4).

Human Exposure Cases: Number of Substances

As shown in Table 34, a single substance was implicated in 8 reported human exposures, and 9 patients were exposed to two or more drugs or products. The 2 reports of death involved exposure to 2 or more drugs or products. For cases that involved multiple substances, the route of exposure is only captured for one of the substances; therefore, the reported case may include additional fentanyls that are not oral or inhalation formulations and may not be limited to the class of immediate-release fentanyls.

Table 34: Number of Substances Involved in Human Exposure Cases Associated with TIRF Medicines or a Fentanyl with Oral or Inhalation as Route of Exposure: 29 October 2012 to 28 October 2013

Number of Substances	Case Count N (%)	Fatality Case Count[a] N (%)
1	8 (47.1%)	0
2	3 (17.6%)	1 (50.0%)
3	3 (17.6%)	1 (50.0%)
4	3 (17.6%)	0
Total	**17 (100.0%)**	**2 (100.0%)**

[a] Includes cases with relative contribution to fatality of 1-Undoubtedly responsible, 2-Probably responsible, or 3-Contributory. This excludes reports with outcome of Death INDIRECT.

Reason for Exposure

The reasons for both unintentional (general and misuse) and intentional (abuse, suspected suicide, and unknown) human exposures associated with TIRF medicines are shown in Table 35. There were 3 cases classified as unintentional exposures with 14 classified as intentional exposures including 4 cases of abuse and 5 suspected suicides.

Table 35: Reason for Human Exposure Cases Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Reason Category	Case Count N (%)
Unintentional	
Unintentional – General	2 (66.7%)
Unintentional - Therapeutic error	1 (33.3%)
Subtotal	**3 (17.6%)**
Intentional	
Intentional – Abuse	4 (28.6%)
Intentional – Misuse	1 (7.1%)
Intentional - Suspected suicide	5 (35.7%)
Intentional – Unknown	2 (14.3%)

Table 35: Reason for Human Exposure Cases Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Reason Category	Case Count N (%)
Unknown reason	2 (14.3%)
Subtotal	**14 (82.4%)**
Total	**17 (100.0%)**

Therapeutic Errors

There was 1 report of a therapeutic error associated with TIRF medicines in the current reporting period (AAPCC Database Table 6B) as shown in Table 36. The therapeutic error was a health professional iatrogenic error in one patient >19 years of age.

Table 36: Distribution of Therapeutic Errors[a] by Age Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Scenario	<6 years (Row %)	6-12 years (Row %)	13-19 years (Row %)	>19 years (Row %)	Unknown Child (Row %)	Unknown Adult (Row %)	Unknown (Row %)	Total [a]
Incorrect Dosing Route	0	0	0	0	0	0	0	0
Dispensing Cup Error	0	0	0	0	0	0	0	0
10-Fold Dosing Error	0	0	0	0	0	0	0	0
Inadvertently Took/Given Someone Else's Medication	0	0	0	0	0	0	0	0
Inadvertently Took/Given Medication Twice	0	0	0	0	0	0	0	0
Incorrect Formulation or Concentration Given	0	0	0	0	0	0	0	0
Incorrect Formulation or Concentration Dispensed	0	0	0	0	0	0	0	0
Wrong Medication Taken/Given	0	0	0	0	0	0	0	0
Health Professional Iatrogenic Error	0	0	0	1 (100.0%)	0	0	0	1
Exposure Through Breast Milk	0	0	0	0	0	0	0	0
More Than One Product Containing Same Ingredient	0	0	0	0	0	0	0	0
Medication Doses Given/Taken Too Close Together	0	0	0	0	0	0	0	0
Confused Units Of Measure	0	0	0	0	0	0	0	0
Other Incorrect Dose	0	0	0	0	0	0	0	0
Drug Interaction	0	0	0	0	0	0	0	0
Other/Unknown Therapeutic Error	0	0	0	0	0	0	0	0

[a] All cases with a scenario category of therapeutic error regardless of reason.

Reason of Exposure by Age

Intentional and unintentional exposures by age are shown in Table 37. Most exposures occurred in adults >19 years of age (n=16) and involved 11 intentional exposures, 3 unintentional exposures, and 2 exposures for an unknown reason. There was 1 intentional exposure in a teenager 13 to 19 years of age.

Table 37: Distribution of Reason for Exposure by Age Associated with TIRF Medicines: 29 October 2012 to 28 October 2013

Reason	<6 years	6-12 years	13-19 years	>19 years	Unknown Child	Unknown Adult	Unknown Age	Missing	Total
Unintentional	0	0	0	3	0	0	0	0	**3**
Intentional	0	0	1	10	0	1	0	0	**12**
Unknown reason	0	0	0	2	0	0	0	0	**2**
Total	**0**	**0**	**1**	**15**	**0**	**1**	**0**	**0**	**17**

Route of Exposure

Ingestion was the route in 10 of 20 exposures associated with TIRF medicines (Table 38). Each exposure case may have more than one route.

Table 38: Route of Exposure for Human Exposure Cases: 29 October 2012 to 28 October 2013

Route	Human Exposures	Fatal Exposures[a]
Ingestion	10	0
Unknown	5	4
Parenteral	3	0
Inhalation/nasal	2	0
Total	**20[b]**	**4[c]**

[a] Includes cases with relative contribution to fatality of 1-Undoubtedly responsible, 2-Probably responsible, or 3-Contributory. This excludes reports with outcome of Death INDIRECT.

[b] Each exposure case may have more than one route listed and patients may have multiple exposures to differing types of fentanyl products. Each exposure and its route(s) counted in this table.

[c] Two patients each had an exposure to 2 different types of fentanyl products. The medical outcome for all exposures was "death." Each exposure is counted in the table.

Medical Outcome

Table 39 displays the medical outcome of human exposure cases associated with TIRF medicines distributed by age. A greater number of severe medical outcomes (major, 5; death 2) was observed in the age group >19 years.

Table 40 compares medical outcome and reason for exposure and shows a higher frequency of serious outcomes in intentional (n=12) versus unintentional exposures (n=3).

Table 39: Medical Outcome of Human Exposure Cases by Patient Age: 29 October 2012 to 28 October 2013

Outcome	<6 years N (%)	6-12 years N (%)	13-19 years N (%)	>19 years N (%)	Unknown Child N (%)	Unknown Adult N (%)	Unknown Age N (%)	Total N (%)
No effect	0	0	0	0	0	0	0	0
Minor effect	0	0	1 (100.0%)	2 (13.3%)	0	0	0	3 (17.6%)
Moderate effect	0	0	0	4 (26.7%)	0	0	0	4 (23.5%)
Major effect	0	0	0	5 (33.3%)	0	0	0	5 (29.4%)
Death[a]	0	0	0	2 (13.3%)	0	0	0	2 (11.8%)
No follow-up, nontoxic	0	0	0	0	0	0	0	0
No follow-up, minimal toxicity	0	0	0	1 (6.7%)	0	0	0	1 (5.9%)
No follow-up, potentially toxic	0	0	0	1 (6.7%)	0	1 (100.0%)	0	2 (11.8%)
Unrelated effect	0	0	0	0	0	0	0	0
Confirmed nonexposure	0	0	0	0	0	0	0	0
Death, indirect report	0	0	0	0	0	0	0	0
Total	**0**	**0**	**1 (5.9%)**	**15 (88.2%)**	**0**	**1 (5.9%)**	**0**	**17 (100.0%)**

[a] Two patients each had an exposure to 2 different types of fentanyl products. The medical outcome for all exposures was "death." Each patient is only counted once in the table.

Table 40: Medical Outcome by Reason for Exposure in Human Exposures: 29 October 2012 to 28 October 2013

Outcome	Unintentional N (%)	Intentional N (%)	Other N (%)	Unknown N (%)	Total N (%)
No effect	0	0	0	0	0
Minor effect	0	3 (25.0%)	0	0	3 (17.6%)
Moderate effect	1 (33.3%)	3 (25.0%)	0	0	4 (23.5%)
Major effect	1 (33.3%)	4 (33.3%)	0	0	5 (29.4%)
Death[a]	0	0	0	2 (100.0%)	2 (11.8%)
No follow-up, nontoxic	0	0	0	0	0
No follow-up, minimal toxicity	0	1 (8.3%)	0	0	1 (5.9%)
No follow-up, potentially toxic	1 (33.3%)	1 (8.3%)	0	0	2 (11.8%)
Unrelated effect	0	0	0	0	0
Confirmed nonexposure	0	0	0	0	0
Death, indirect report	0	0	0	0	0
Total	**3 (17.6%)**	**12 (70.6%)**	**0**	**2 (11.8%)**	**17 (100.0%)**

[a] Two patients each had an exposure to 2 different types of fentanyl products. The medical outcome for all exposures was "death." Each patient is counted once in the table.

8 PERIODIC SURVEYS OF STAKEHOLDERS

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers', pharmacists', and prescribers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the educational materials for all stakeholders, enrollment form (pharmacists and prescribers only), Full Prescribing Information (pharmacists and prescribers only) and medication guides (prescribers and patients) of each product and the PPAF (prescribers and patients only). The protocols describe the administration of the individual surveys that were conducted among patients, prescribers, and pharmacists who are treated with TIRF medicines, or their caregivers (see Appendix 12.4.1, 12.4.2, and 12.4.3, respectively, for the patient, pharmacist, and prescriber survey protocols).

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

8.1 Patient KAB Survey

8.1.1 Survey Statistics

Patients were recruited through a pharmacy network partner and a PBM. Physician recruitment of patients did not result in any completed surveys. Based on the number of prescriptions filled during the 120 days prior to survey implementation (16 September 2013), the national pharmacy chain network partner identified 1,450 possible participants and the PBM identified 453 possible participants among patients and caregivers. All of these possible participants were sent a survey invitation letter. A total of 2,454 follow up letters were sent to non-responders (some potential participants received more than one reminder letter). Of the 1,903 possible participants, 347 respondents accessed the survey and were screened for eligibility; 302 of the 347 (87.0%) respondents met eligibility criteria and completed the survey; 175 (58.0%) completed the survey online, and 127 (42.1%) completed it by telephone. From the 302 respondents, 303 surveys were collected. It was identified that one respondent completed the survey twice. Only the first completed survey was included in the analysis for this report.

Of the 347 respondents, the screening procedure identified 302 eligible participants (including 301 patients and 1 caregiver) all of whom completed the survey. Due to the small (n=1) number of caregivers participating in the survey, the majority of results are reported for patients and caregivers combined.

A total of 346 patients/caregivers agreed to participate in this survey. The screening process found 44 respondents were not eligible to participate: 16 (4.6%) respondents were ineligible because they had previously participated in a survey about TIRF medicines; 11 (3.2%) because they did not know if they had previously participated; 15 (4.3%) said "No" when asked if they were caregivers for someone who has filled a prescription for a TIRF medicine within the

preceding 4 months; 1 (0.3%) respondent because he/she, or an immediate family member, had worked for a TRIG company in the past, and 1 (0.3%) did not know whether he/she, or an immediate family member, had worked for a TRIG company, United BioSource Corporation, RelayHealth, McKesson Specialty Care Solutions, or the FDA in the past and thus were considered ineligible. Thus, there were 302 eligible participants (including one caregiver), all of whom completed the survey.

Those taking the survey online took an average of 14.7 minutes to complete it, while those taking it by telephone took an average of 20.1 minutes.

8.1.2 Demographics and Respondent Characteristics

Most (n=126; 41.7%) respondents were in the 50 – 59 years age group; 184 (60.9%) were females, and 243 (80.5%) respondents had at least some college or Associate's degree or higher education. Most prescriptions filled in the 4 months preceding the survey included 117 (38.7%) for Actiq® (including generic versions), 107 (35.4%) for Fentora®, and 88 (29.1%) for Subsys®. Participants were largely from the Northeast (n=113; 37.4%) and 133 (44.0%) from the South regions of the US.

8.1.3 TIRF Educational Materials

Of the 302 respondents, 283 (93.7%), reported they had received the Medication Guide for the TIRF medicine prescribed to them; 150 (53.0%) reported receiving the Medication Guide from their doctor with 117 (78.0%) receiving it at the first appointment with the prescribing doctor; 254 (89.8%) respondents received it from their pharmacy; 228 (89.8%) respondents recollected receiving the Medication Guide each time a prescription was filled. Most (n=268; 94.7%) recollected reading the Medication Guide; 170 (63.0%) read all of it with 126 (46.7%) of them understanding all or most (n=125; 46.3%) of the Medication Guide. The pharmacist (n=147; 84.5%) or the prescriber (n=114; 65.5%) offered to explain the Medication Guide to respondents.

After respondents were asked the questions regarding the key risk messages, they were asked if they had received, read, and understood the Patient-Prescriber Agreement Form (PPAF). A total of 223 (73.8%) respondents indicated that someone at the doctor's office had offered to explain the PPAF to them, and that 175 (78.5%) of them understood all of it and 42 (18.8%) understood most of it. The PPAF was signed by 222 (73.5%) respondents; of these 222 responders, 151 (68.0%) reported receiving a copy of the signed PPAF.

8.1.4 Patient Survey Results

8.1.4.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's knowledge that TIRF medicines can cause life-threatening breathing problems that can lead to death.

Analysis of a question for Key Risk Message 1 showed that 272 (90.1%) of the 302 eligible respondents were aware of the risk of life-threatening breathing problems with TIRF medicines.

8.1.4.2 Key Risk Message 2

Key Risk Message 2 refers to the respondents' knowledge that they should not take TIRF Medicines if they are not opioid tolerant. Three questions defined this key risk message.

In response to the statement that TIRF medicines should only be taken by patients who are opioid tolerant, 277 (91.7%) respondents gave the correct (True) response.

The majority (n=267; 88.4%) of respondents understood that opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines. Two-hundred-and-six respondents (68.2%) knew that it is not okay for patients to take TIRF medicines for headache pain, while 75 (24.8%) respondents selected the "I don't know" option. Of the 206 respondents who answered false to *"It is OK for patients to take TIRF medicines for headache pain"*, 176 respondents had read most of the Medication Guide and 30 respondents had read some or none of it.

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.5 (CI 2.3, 3.0) out of a possible 3.

8.1.4.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider. Three questions define this key risk message.

A total of 103 (34.1%) respondents understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine while 112 (37.1%) selected the "I don't know" option. Of the 103 respondents who gave the correct response, 95 (92.2%) read most of the Medication Guide while 8 (7.8%) read some or none of the Medication Guide. Of the 87 respondents who answered this question incorrectly, 74 (85.1%) had read most of the Medication Guide and of the 112 (37.1%) respondents who selected the "I don't know" response, 79 (70.5%) had read the Medication Guide.

Responding to Question 13c, 301 (99.7%) understood that TIRF medicines should be taken exactly as prescribed by the doctor, and 252 (83.4%) knew that is not all right to take TIRF medicines for short-term pain that will go away in a few days.

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.2 (CI 2.0, 3.0) out of a possible 3.

8.1.4.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's knowledge that they must not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

Of the 302 respondents, 285 (94.4%) respondents understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

8.1.4.5 Key Risk Message 5

Key Risk Message 5 refers to the patient's knowledge that TIRF medicines should not be given to anyone else even if they have the same symptoms.

A total of 296 (98.0%) respondents understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient, and 297 (98.3%) understood that selling or giving away TIRF medicines is against the law.

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.0 (CI 1.8, 2.0) out of a possible 2.

8.1.4.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed.

All 302 respondents selected the correct response regarding TIRF medicines being stored in a safe place out of the reach of children. Of the 302 respondents, 285 (94.4%) understood that TIRF medicines must be disposed of as described in the specific product's Medication Guide. Most (n=275; 91.1%) respondents understood that a TIRF medicine can cause an overdose and death in any child who takes it; and that they should get emergency help right away (n=264; 87.4%) (*What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine?*).

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.7 (CI 3.5, 4.0) out of a possible 4.

8.1.5 Additional Safety Questions about TIRF Medicines Safety

Additional questions were asked to assess whether the patient had been informed of the risks and possible side effects, indications, usage, and storage, and the availability of TIRF medicines through the TIRF REMS Access Program. This section summarizes the respondents' answers to some components associated with key risk messages and additional survey questions not associated with key risk messages.

An HCP from the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine with 259 (85.8%) of respondents while 36 (11.9%) respondents did not recall having this conversation.

Most respondents understood that TIRF medicines should not be used for headache or migraine pain (n=234; 77.5%), dental pain (n=264; 87.4%), and pain after surgery (n=207; 68.5%). Only 66 (21.9%) respondents were aware that TIRF medicines are not indicated for long-lasting painful conditions not caused by cancer. Whereas, 194 (64.2%) respondents knew that TIRF medicines might be used for BTP from cancer.

Most (n=281; 93.0%) respondents recollected that someone in the doctor's office explained the proper way of using the prescribed TIRF medicines while 241 (79.8%) respondents were educated by someone in the doctor's office regarding the proper storage of the prescribed TIRF medicines.

Most (n=285; 94.4%) respondents were aware of the proper way to dispose of TIRF medicines as described in the prescribed product's Medication Guide. However, the awareness that TIRF medicines are only available through the TIRF REMS Access Program was low with 147 (48.7%) selecting the correct response. Most respondents (n=275; 91.1%) understood that a TIRF medicine might cause overdose and death in any child who takes it.

Overall, the results indicate that respondents were aware of most of the precautions needed to ensure safe use of TIRF medicines. Taking into account the percentage of incorrect and "I don't know" responses, patients/caregivers scored somewhat less with regard to the need to stop taking TIRF medicines if the around-the-clock opioid is stopped and the approved indication for TIRF medicines.

8.1.6 Analysis of Sub-populations

To assess further patients' understanding of key risk messages, sub-group analyses with more than 20 respondents were conducted.

Of the 248 respondents who read most of the Medication Guide (sub-group S-1a), 234 (94.4%) understood Key Risk Message 1 (*TIRF medicines can cause life-threatening breathing problems that can lead to death*) compared with 38 of the 54 (70.4%) who read some or none of the Medication Guide (sub-group S-1b).

In the case of Key Risk Message 2, 230 (92.7%) respondents who read most of the Medication Guide and 47 (87.0%) of respondents who read some or none of the Medication Guide were aware that TIRF medicines should only be taken by patients who are opioid tolerant. In addition, 221 (89.1%) respondents who read most of the Medication Guide (sub-group S-1a) and 46 (85.2%) of sub-group S-1b respondents understood the meaning of the term opioid tolerant. Most (n=176; 71.0%) respondents of sub-group S-1a correctly answered that TIRF medicines are not recommended for headache pain compared with 30 of 54 (55.6%) of sub-group S-1b respondents.

Of the three questions/statements under Key Risk Message 3, 95 (38.3%) of sub-group S-1a and 8 (14.8%) sub-group S-1b respondents gave the correct response to Question 12b (*If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine*). Almost all (n=247; 99.6%) of sub-group S-1a and 54 (100.0%) of sub-group S-1b respondents correctly identified with the statement that TIRF medicines should be taken exactly as prescribed by the doctor; and 214 (86.3%) of sub-group S-1a and 38 (70.4%) of sub-group S-1b disagreed with the statement that it is okay to take TIRF medicines for short-term pain that will go away in a few days.

There was high understanding for Key Risk Message 4 Question 12c (*It is safe to switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider first*) because 233 (94.0%) of sub-group S-1a and 52 (96.3%) of sub-group S-1b responded correctly.

Almost all respondents understood Key Risk Message 5 that patients should not give TIRF medicines to anyone else even if they have the same symptoms.

Respondents demonstrated a high level of understanding for Key Risk Message 6 that TIRF medicines should be stored in a safe place away from children and properly disposed.

Overall, the results indicate that respondents who read all or most of the Medication Guide were better informed regarding the safe use of TIRF medicines. Therefore, the Medication Guide is an effective tool to help patients understand the key risk messages based on the goals of the TIRF REMS. All other sub-group analyses showed that the results are similar to the results in the primary population, and no sub-group-related trends were evident.

8.2 Pharmacy KAB Survey

8.2.1 Survey Statistics

A total of 7,167 pharmacists were invited to participate in this survey. Of those invited to participate, 5,982 were outpatient pharmacists, 860 were inpatient pharmacists, and 325 were pharmacists practicing in Closed System Pharmacies (CSPs). Some pharmacists received more than one reminder.

From the total 403 respondents, 300 pharmacists met eligibility criteria and completed the survey. Of these 300 pharmacists, 291 (97.0%) completed the survey online, and 9 (3.0%) completed it by telephone. Of the 300 pharmacists who completed the survey, 4 were CSP pharmacists, 15 were inpatient pharmacists, and 281 were outpatient pharmacists.

A total of 371 pharmacists agreed to participate in this survey, 339 of these pharmacists stated they had not taken part in the survey about TIRF medicines before, and 304 of these pharmacists worked in pharmacies that were enrolled in the TIRF REMS. Of the 372 total respondents, 68 were ineligible to participate in the survey because they either did not agree to participate, indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before, or worked in pharmacies that were not enrolled or they did not know whether their pharmacy was enrolled in the TIRF REMS. Of the 304 respondents who reported that their pharmacies were enrolled in the TIRF REMS Access Program, 1 respondent was ineligible for the survey because the respondent, or an immediate family member, had worked for a TRIG company in the past, 1 was ineligible because the respondent or an immediate family member, had worked for the FDA in the past, and 2 respondents preferred not to answer the question.

Those taking the survey online took an average of 14.3 minutes to complete it, while those taking it by telephone took an average of 18.0 minutes.

8.2.2 Demographic and Respondent Characteristics

The majority of pharmacists who completed the survey were male (183, 61.0%), and out of 300 eligible pharmacists, 157 (52.3%) had been a practicing pharmacist for more than 15 years. Respondents from the South, Northeast, and Midwest reflected 32.3%, 26.0%, and 24.0% of total respondents, respectively, while respondents from the Western region of the US composed 17.3% of total respondents. The proportion of respondents who completed the survey within each geographic region was similar to the overall proportion of pharmacies enrolled in the TIRF REMS Access Program as of 10 October 2013 in each geographic region. There were no respondents from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

Most pharmacists (242, 80.7%) functioned as the pharmacist-in-charge for the TIRF REMS Access Program where they worked, and a majority of pharmacists (235, 78.3%) had dispensed a TIRF medicine zero to 2 times per month within the past 6 months. The most frequently dispensed TIRF medicine within the 6 months prior to taking the survey was Actiq® or generic Actiq (120 pharmacists, 77.4%).

8.2.3 TIRF Educational Materials

Pharmacists were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide. Almost all pharmacists reported they had received or had access to the Full Prescribing Information and the Medication Guide (291, 97.0%; and 297, 99.0%, respectively). Of those with access to these materials, 76.6% and 84.2%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide.

There were 18 respondents who typed a response into the free text field for Question 22 (*Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?)*. Of the 18 responses, 13 were requests for medical information and 5 were indications the free text field was not applicable or they had no questions.

8.2.4 Pharmacy Survey Results

8.2.4.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines.

Analysis of responses to components of Key Risk Message 1 showed that a high percentage of pharmacists knew that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer (271, 90.3%), and are those who are currently taking opioid therapy (242, 80.7%). Somewhat less understood was

cancer patients with no known contraindications to the drug fentanyl, but who are not currently taking around-the-clock opioid therapy are not considered opioid tolerant (228, 76.0%).

A high percentage of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients (86.0%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (93.7%). Similarly, 248 (82.7%) pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product, and that TIRF medicines may not be used to treat opioid non-tolerant patients (82.0%). Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 5.9 (CI 5.7, 7.0) out of a possible 7.

8.2.4.2 Key Risk Message 2

Key Risk Message 2 refers to the pharmacist's knowledge of the approved indications for prescribing TIRF medicines to opioid tolerant patients.

Responses to components of Key Risk Message 2 indicate that 268 (89.3%) pharmacists were aware that TIRF medicines are indicated for opioid-tolerant patients with BTP from cancer and not for patients with acute or postoperative pain (84.7%), headache or migraine pain (92.3%), or dental pain (96.7%). Only 47.0% of pharmacists correctly responded that TIRF medicines are not indicated for chronic non-cancer pain.

Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 4.1(CI 3.9, 5.0) out of a possible 5.

8.2.4.3 Key Risk Message 3

Key Risk Message 3 refers to the pharmacist's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Responses to components of Key Risk Message 3 showed that 290 (96.7%) pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines; a personal history of past or current alcohol or drug abuse or family history of drug and alcohol abuse is a risk factor for opioid abuse (99.0%); and TIRF medicines can be abused in a manner similar to other opioid agonists (94.0%). Somewhat less understood was that a personal history of psychiatric illness is a risk factor for opioid abuse (72.0%). Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 3.6 (CI 3.4, 5.0) out of a possible 4.

8.2.4.4 Key Risk Message 4

Key Risk Message 4 refers to the pharmacist's knowledge that TIRF medicines are not interchangeable regardless of the route of administration.

Responses to questions tied to Key Risk Message 4 showed that 284 pharmacists understood TIRF medicines are not interchangeable with each other regardless of the route of administration (94.7%); the conversion of 1 TIRF medicine to another may result in a fatal overdose (92.0%); and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (91.3%).

Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 2.8 (CI 2.6, 3.0) out of a possible 3.

8.2.5 Additional Safety Questions about TIRF Medicines Safety

Additional questions about TIRM Medicines generally confirmed the pharmacists' understanding of the safety issues and the risks associated with taking TIRF medicines.

Question 6 was added for this 24-month KAB survey to assist in determining the pharmacist understanding of around-the-clock usage, and 65.3% of pharmacists correctly indicated that a cancer patients should not started on a TIRF medicine and an around-the-clock opioid at the same time, and 74.7% understood a cancer patient who had been on an around-the-clock opioid for 1 day should not start taking a TIRF medicine for BTP. Overall, greater than 70% of pharmacists correctly identified an opioid drug/dose regimen that when taken by the patient, identifies patients as opioid tolerant according to the labeling for TIRF medicines. However, fewer understood that an equianalgesic dose of another oral opioid could also meet the definition of opioid tolerant (correct response 59.0%).

Pharmacists correctly indicated that TIRF medicines may not be sold, loaned, or transferred to another pharmacy (91.3%); pharmacy staff who dispense TIRF medicines must be educated on the requirements of the TIRF REMS Access Program (94.0%); and that TIRF medicines with the same route of administration cannot be substituted with each other (96.3%).

Thirteen (86.7%) inpatient pharmacists correctly indicated that it is not appropriate to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for home use.

8.2.6 Pharmacist Activities When Dispensing TIRF Medicines

Pharmacists were asked about specific activities performed when dispensing TIRF medicines Of the 300 eligible pharmacists, 167 (55.7%) responded they always ask their patients (or a patient's caregiver) about the presence of children in the home; 18.0% responded they ask only with the first prescription. Additionally, 69.3% responded they always instruct the patient (or their caregivers) not to share TIRF medicines, 66.0% responded they always counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal, 74.3% responded they always instruct patients (or their caregivers) to keep TIRF medicines out of reach of children, 66.0% responded they always instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines, and 91.3% responded they always give patients (or their caregivers) the Medication Guide for TIRF medicine(s).

8.3 Prescriber KAB Survey

8.3.1 Survey Statistics

A total of 5,108 prescribers were sent letters inviting them to participate in this survey. An additional 11,986 reminder letters were sent. Some prescribers may have received more than 1 reminder letter.

In all, a total of 425 prescribers expressed interest in the survey and were screened for eligibility. The number of respondents found eligible for participating in the survey was 302, all of whom completed the survey. Of the 302 respondents, 289 (95.7%) completed the survey online, and 13 (4.3%) completed it by telephone. There were no duplicate respondents.

Based on the TRIG Sponsors interpretation of state laws regarding prescriber reimbursement, respondents from Massachusetts (MA), Vermont (VT), and Minnesota (MN) were eligible to participate in the survey; however, were not eligible to receive the $125 honorarium. Letters were sent to prescribers in these states, and 2 respondents from MA chose to participate despite receiving no honorarium.

A total of 425 prescribers agreed to participate in this survey and of those 302 prescribers were enrolled in the TIRF REMS Access program; 49 (11.5%) prescribers were ineligible because they were not enrolled in the program or they did not know whether they were enrolled. Seventeen (4.0%) respondents were ineligible because they had previously taken part in the survey about TIRF medicines and 49 (11.5%) respondents did not know if they had participated; therefore, they were considered ineligible. Five respondents were ineligible for the survey because they, or an immediate family member, had worked for UBC or a TRIG company in the past, or did not know whether they, or an immediate family member, had worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or the FDA in the past, and 1 prescriber preferred not to answer and thus was considered ineligible.

Those taking the survey online took a mean of 17.0 minutes to complete, while those taking it by telephone took a mean of 27.0 minutes.

8.3.2 Demographics and Respondent Characteristics

The survey included 27.5% respondents from the Northeast, 15.2% from the Midwest, 33.1% from the South, and 23.5% from the Western region of the US. The proportion of eligible completed prescribers within each geographic region was similar to the overall proportion of prescribers (9,042 prescribers enrolled in the TIRF REMS Access Program as of 19 October 2013) in each geographic region. There were no respondents from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

The most common healthcare degree was an MD (60.3%), and the most common medical specialties were pain management (49.0%) and oncology (22.8%). Of respondents who were medical doctors, 117 of the respondents (38.7%) had practiced medicine for more than 15 years.

The survey results showed that 173 (57.3%) of the prescribers recalled prescribing TIRF medicines 1 to 2 times a month within the 6 months preceding the survey, and Actiq® or generic Actiq were the most frequently prescribed TIRF medicine (74.2% of prescribers) followed by Fentora® at 58.5% of prescribers.

8.3.3 TIRF Educational Materials

Prescribers were asked about their awareness of educational materials for TIRF medicines, specifically the Full Prescribing Information the Medication Guide, and the Patient-Prescriber

Agreement Form (PPAF). Most (n=282; 93.4%) respondents had received or had access to the Full Prescribing Information and 273 (90.4%) to the Medication Guide. Of those with access to these materials, 86.2% and 90.1%indicated that they had read the Full Prescribing Information and the Medication Guide, respectively. Additionally, most prescribers reported reviewing the PPAF with each patient or their caregiver (86.8%); signing the PPAF and having the patient/caregiver sign the PPAF (92.4%); and giving a copy of the PPAF to the patient (80.5%).

8.3.4 Prescriber Survey Results

8.3.4.1 Key Risk Message 1

Key Risk Message 1 assesses the prescriber's knowledge of the specific contraindications for TIRF medicines in patients.

Analysis of responses to questions tied to Key Risk Message 1 showed that a high percentage of prescribers understand that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur (n=265; 87.7%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (n=283; 93.7%). Most prescribers were aware patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (n=244; 80.8%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (n=242; 80.1%). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 6.0 (CI 5.8, 7.0) out of 7.

8.3.4.2 Key Risk Message 2

Key Risk Message 2 assesses the prescriber's knowledge of the approved indications for prescribing TIRF Medicines to opioid tolerant patients.

Responses to components of Key Risk Message 2 indicate that a high percentage of respondents prescribe TIRF medicines for the approved indication of treatment of breakthrough cancer pain in opioid-tolerant patients (n=279; 92.4%) and not for patients with acute or postoperative pain (5.6%), headache or migraine pain (6.6%), or dental pain (1.7%).

Respondents were presented with descriptions of 4 patients experiencing BTP and asked them to select the case that should not receive a TIRF medicine. The correct response was given by 199 (65.9%) prescribers.

8.3.4.3 Key Risk Message 3

Key Risk Message 3 assesses the prescriber's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Key Risk Message 3 showed that a high percentage of prescribers were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines (99.0%), a personal history of psychiatric illness is a risk factor for opioid abuse (82.8%), a personal history of past or current alcohol or drug abuse or family history of drug and alcohol abuse is a risk factor for opioid abuse (99.0%), and that TIRF medicines can be abused in a manner similar to

other opioid agonists (96.4%). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.8 (CI 3.6, 4.0) out of 4.

8.3.4.4 Key Risk Message 4

Key Risk Message 4 assesses the prescriber's knowledge that TIRF medicines are not interchangeable regardless of the route of administration.

Majority of prescribers (279, 92.4%) understood that TIRF medicines are not interchangeable with each other regardless of the route of administration, that the conversion of 1 TIRF medicine to another may result in a fatal overdose (n=286; 94.7%), and that dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (n=274; 90.7%). A large number of prescribers (225, 74.5%) correctly responded that conversion must not be done on a microgram-to-microgram basis. Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.5 (CI 3.3, 4.0) out of 4.

8.3.5 Additional Questions about TIRF Medicines Safety

Over half of the (n=183; 60.6%) prescribers correctly identified that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time, while 105 (34.8%) prescribers believe such a combination is acceptable; 196 (64.9%) of prescribers correctly indicated that a cancer patient who has been on an around-the-clock opioid for 1 day should not start taking a TIRF medicine for BTP; 160 (53.0%) responded that patients should not continue to take TIRF medicines if they stopped taking their around-the-clock opioid medicine.

A majority of prescribers correctly identified the description of opioid-tolerant patients by the listed opioid preparations and corresponding doses as 8 mg oral hydromorphone/day (68.5%), 60 mg oral morphine/day (89.1%), 30 mg/day oral oxycodone (76.2%), 25 mcg transdermal fentanyl/hour (80.8%), 25 mg/day oral oxymorphone (69.9%), and an equianalgesic dose of another oral opioid (65.9%).

Most prescribers (n=254; 84.1%) correctly indicated that for a patient starting titration with a TIRF medicine, an appropriate dose is the lowest available dose, unless the Full Prescribing Information provides specific guidance (84.1%). When a prescriber has started titrating a patient with the lowest dose of a TIRF medicine, and, after 30 minutes, the BTP has not been sufficiently relieved, 205 (67.9%) prescribers correctly pointed out that guidance should be based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

Response to Question 17 demonstrates that the majority (225, 74.5%) of prescribers have a high level of understanding pertaining to the safe use of a TIRF medicine with a CYP3A4 inhibitor and the need for monitoring the dosage for their patient. Further, this data reflects that the prescribers clearly understand the need to carefully monitor the patient for opioid toxicity to avoid any potential cause for fatal respiratory depression.

Of the 302 respondents who completed the survey, 199 (65.9%) correctly stated that a patient who had a mastectomy and reconstructive surgery for localized breast cancer with persistent cancer pain managed with 30 mg/day oral morphine for 6 weeks should not receive TIRF medicines because the patient does not meet the definition of opioid tolerant. Furthermore, the majority (225, 74.5%) of prescribers correctly indicated that the prescriber must not convert a patient to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties which could result in a fentanyl overdose.

Nearly all prescribers surveyed (n=298; 98.7%) understood that TIRF medicines contain fentanyl in an amount that could be fatal for children of all ages, for individuals for whom they were not prescribed, and for those who are not opioid tolerant. Two hundred and seventy-eight (92.1%) prescribers were aware that patients must be informed that TIRF medicines should not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain. One hundred and seventy-five (57.9%) prescribers understood that patients should be instructed not to continue their TIRF medicines if they stop taking their around-the-clock opioid medicine; 299 (99.0%) agreed that patients must be instructed not to share their TIRF medicine with anyone else, even if that person has the same symptoms; and 160 (53.0%) indicated that if patients stop taking their around-the-clock opioid pain medicine, they must stop taking their TIRF medicine.

8.3.6 Prescriber Activities When Prescribing TIRF Medicines

More than one-half of prescribers (56.3%) indicated they always ask patients (or their caregivers) about the presence of children in the home. Prescribers take care to instruct patients (or their caregivers) not to share TIRF medicines (n=239; 79.1%). When asked about counseling patients/caregivers that accidental exposure to TIRF medicines by a child might be fatal, 197 (65.2%) prescribers selected “always”, 63 (20.9%) responded “only with first prescription”, and 31 (10.3%) answered “sometimes”. In response to the question about instructing patients/caregivers to keep TIRF medicines out of the reach of children, 220 (72.8%) selected “always,” 46 (15.2%) selected “only with the first prescription”, and 28 (9.3%) selected “sometimes.” With regard to instructing patients/caregivers about proper disposal of any unused or partially used TIRF medicines, 187 (61.9%) answered “always,” 62 (20.5%) answered “only with the first prescription,” and 37 (12.3%) responded “sometimes.”

Less than one-half of prescribers (47.0%) always give patients/caregivers the Medication Guide for their TIRF medicine, and 35.8% give their patients/caregivers the Medication Guide for their TIRF medicine with the first prescription.

8.3.7 Analyses of Sub-populations

Of the 13 respondents who completed the survey via telephone, the correct response rate when asked to identify patients with cancer who are considered opioid-tolerant was 53.8% (n=7) by selecting the “False” response: “*Who are not currently taking opioid therapy, but have taken opioid therapy before*”(Key Risk Message 1) compared with the correct response rate of 89.6% for those who used the Internet. Likewise, 7 (53.8%) telephone respondents correctly selected the “False” response: “*Who have no known contraindications to the drug fentanyl, but are not*

currently taking around-the-clock opioid therapy" (Key Risk Message 1) compared with 83.4% in the sub-group that used the Internet.

Of the 35 prescribers who had not read the Medication Guide or Full Prescribing Information, 24 (68.6%) were aware that TIRF medicines may not be used in opioid non-tolerant patients (Question 7c; Key Risk Message 1) compared with 218 (81.6%) prescribers who read the Medication Guide or PI.

Of the 35 respondents, 23 (65.7%) had not read the Medication Guide or the Full Prescribing Information correctly identified "a personal history of psychiatric illness" as a risk factor for opioid abuse (Question 8a, Key Risk Message 1) compared with 85.0% among those who had read the Medication Guide or PI).

Respondents who completed the survey in less than 10 minutes had a low correct response rate of 57.4% when asked about prescribing an alternate TIRF medicine that is not a bioequivalent generic version of the branded product (Question 14, Key Risk Message 4) compared with the more than 75% correct response rate among those who longer to complete the survey.

8.4 Overall Conclusions for KAB Results

During the 12-month reporting period TRIG established a threshold for each response rate of <65%. The purpose of this threshold was to assist TRIG in tracking and monitoring the data for each key risk message across each wave ultimately providing direction in determining which area(s) would require improvement to ensure the patient/caregiver, pharmacist and prescriber KAB surveys were meeting the goals of the REMS.

Patients:
The specific goal of the TIRF medicines patient KAB survey was to evaluate the level of understanding by patients and caregivers of the risks associated with use of TIRF medicines, the importance of being opioid tolerant before starting a TIRF medicine, strictly following the directions of the HCP, not switching from one TIRF medicine to another medicine that contains fentanyl without talking to an HCP, the importance of patients not giving TIRF medicines to anyone else even if they have the same symptoms, and storing TIRF medicines in a safe place away from children and proper disposal of unused medicine.

Revisions were made to the 24-month survey based on feedback received from the FDA on the 12-month assessment. The one item that scored noticeably lower on the 24-month assessment was the concept that patients should stop taking a TIRF medicine if they stop their around the clock opioid. The TRIG is exploring options to increase awareness of this important safety message, which is discussed in the current PPAF and medication guides for each product. While not a key risk message in the prescriber survey, this concept was also a low scoring item for prescribers even though it is conveyed in the Prescriber Education Program as a patient counseling message.

The overall higher level of understanding of the remaining items/questions throughout the 6 key risk messages indicates that patients are knowledgeable about the safe use and storage of TIRF medicines. The higher level of understanding in patients who read most or all of the medication

guide demonstrates effective communication of the key risk messages, which may also be reinforced by prescribers and pharmacists. The consistent high level of patient understanding of key risk messages between the 12-month and 24-month surveys indicates that the REMS goals are being met with the tools currently in place.

Pharmacists:

The specific goal of the TIRF REMS pharmacist KAB survey was to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients.

Based on FDA feedback from the 12-month assessment, revisions were made to the 24-month pharmacist survey. Prior to the 24-month survey, the questions were revised based on the QR results to improve understanding of the questions/items being tested. In addition, there were 22,762 (59%) pharmacies that enrolled or re-enrolled during this reporting period by successfully completing the education program, thereby reinforcing the educational message of the shared system REMS.

In the 24-month survey, only one item was identified as having a low level of understanding among pharmacists (TIRF medicines are not indicated for chronic non-cancer pain; 47.0%). However, it should be noted that there was a marked improvement in the Pharmacist's correct response rate for this concept from the 12-month KAB survey to the 24-month KAB survey. It should also be noted that recognition of uses for which TIRF medicines are not indicated is not a goal of the TIRF REMS for pharmacists. Because a majority of the pharmacists surveyed demonstrated a high level of understanding of all but one item out of the 4 key risk messages, the TRIG has determined that the Pharmacist Education Program is meeting the goals of the TIRF REMS. Therefore, no changes to the education program for pharmacists are required at this time.

Prescribers:

The prescriber KAB survey included responses from 302 TIRF medicine prescribers invited from a random sample of all prescribers enrolled in the REMS. The specific goal of the prescriber KAB survey was to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed.

Following the 12 March 2013 FDA feedback on the 12-month TIRF REMS Access Program Assessment Report, the survey questionnaire was modified.

The concept that a patient must discontinue a TIRF medicine when they stop taking their around-the-clock opioid, while not a key risk message for the prescribers, received a low correct response rate. Prescribers are educated on this concept in the educational program and in the PPAF. Prescriber's low understanding of this concept is likely to have affected the level of

understanding of respondents in the patient survey. The TRIG is exploring options to increase awareness of this important safety message.

The overall higher level of understanding of the remaining items/questions throughout the 4 key risk messages indicates that prescribers are knowledgeable about the safe of TIRF medicines. The consistent high level of prescribers' understanding of key risk messages between the 12-month and 24-month surveys indicates that the prescriber education program is meeting the goals of the TIRF REMS with the tools currently in place.

9 FDA COMMUNICATIONS

In the first quarter of calendar year 2013, the TRIG companies responded to several FDA information requests concerning the 12-month assessment report, with a focus on the metrics for the closed system pharmacies.

Submission of REMS Modification 2 and the establishment of the Drug Master File for the TIRF REMS was completed on 21 October 2013. Modification 2 for the TIRF REMS consisted of the following:

- Revised terminology, processes, and definitions for outpatient pharmacies;
- Revised attestations for physicians and patients to address concerns regarding patient access;
- Revised Program Overview and Frequently Asked Questions to improve clarity and content; and,
- Updated REMS materials to reflect the completion of the transition phase for the TIRF REMS Access Program,

The proposed changes to the TIRF REMS, including the appended REMS materials, were approved on 07 November 2013.

10 POST-APPROVAL STUDIES AND CLINICAL TRIALS

FDA should refer to the most recent periodic safety report from each TIRF sponsor for updated information on post-approval studies and/or clinical trials.

11 OVERALL CONCLUSIONS

The TIRF REMS Access program was approved on 28 December 2011 and successfully launched on 12 March 2012, approximately 11 weeks after approval. This 24-month assessment report covers the timeframe between 29 October 2012 and 28 October 2013.

With an overall volume of more than 111,104 prescriptions authorized for REMS edits during this reporting period and only 1 report of a patient having difficulty accessing an enrolled

prescriber, the program does not appear to present a significant barrier to access of these important medications. The TIRF REMS Access program continues to monitor the electronic systems and stakeholder reports for issues and, where appropriate, corrective actions or system improvements are instituted.

The REMS goal of educating prescribers and pharmacists on the potential for misuse, abuse, addiction, and overdose is being documented through the completion of the Knowledge Assessment, which is required for enrollment. Effectiveness of the educational program is evaluated through the pharmacy and prescriber KAB surveys that are performed prior to each assessment report. Results of the 24-month surveys indicate that the educational program has increased the understanding of safe use of TIRF medicines by pharmacists and prescribers. Key risk messages that are important for these stakeholders to understand include the fact that TIRF medicines are contraindicated in opioid non-tolerant patients, are only indicated for the management of breakthrough pain in adult cancer patients, contain fentanyl with abuse liability similar to other opioid analgesics, and are not interchangeable with each other on a mcg-to-mcg basis regardless of route of administration. Due to the high level of understanding of these concepts by pharmacists and prescribers, no modifications to the educational programs or Knowledge Assessment are recommended at this time.

Patient education is completed through healthcare provider counseling and completion of a PPAF. The patient KAB survey results indicate that the patient-oriented educational materials including the PPAF and Medication Guide for each product are effective tools at communicating safe use messages to patients, including the importance of not sharing TIRF medicines, taking TIRF medicines as prescribed, and properly disposing unused TIRF medicines. One identified area of potential improvement is patient understanding of the need to stop taking TIRF medicines if around-the-clock opioid therapy is stopped. The TRIG is exploring options to increase awareness of this important safety issue, which is discussed in the current PPAF and Medication Guide for each product.

Surveillance data was obtained from AAPCC and FDA AERS for inclusion in this 24-month assessment report as it had been in the previous two assessment reports submitted to FDA. The AAPCC data included no reports of pediatric exposure to TIRF medicines and only one exposure in an adolescent 16 years of age with a minor outcome. Four fatalities were included in the AAPCC data, 2 related to exposure to TIRF medicines and 2 related to exposure to unknown fentanyl products. TRIG is unable to evaluate safety signals based upon these reports at this time. Abstracts or full narratives of all 4 fatalities will be available from the AAPCC in late 2014 at the earliest and will be sent to the FDA as soon as they are received.

FDA AERS data encompassing Q3 and Q4 2012 were the most recent data available for this 24-month assessment report. Sixteen new case reports associated with TIRF medicine exposure were identified in the data set. Eight of the cases included one of the individual PT of Interest for the TIRF REMS or at least one PT from the MedDRA SMQ, *Acute Central Respiratory Depression.* Consistent with the 12 month TIRF REMS Assessment report, signals continue to be seen for the PT of Interest: "Off label Use", "Drug prescribing error" and "Drug withdraw syndrome". When analyzed according to TRIG categories of interest, signals were also

generated for inappropriate use, drug diversion, medication error, and drug dependence. Realizing the limitations and incompleteness of data in the FDA AERS database, and the resulting difficulty in identifying true safety signals from this database alone, FDA has requested that TRIG sponsors provide complete listings of adverse event reports in CIOMS II Line Listing format for this and future assessment reports. In addition, FDA requested MedWatch forms for all cases involving addiction, overdose and death. FDA and TRIG sponsors agreed that this data will be submitted by each individual company no later than the end of January 2014. FDA AERS data will not be included in future TIRF REMS assessment reports.

Based on the data provided in this report the TRIG concludes that the REMS is meeting its established goals. The improvement in knowledge demonstrated by pharmacists and prescribers and the continued high level of awareness of most key risk messages by patients provides evidence that the current tools are effectively communicating the important safety messages to key stakeholders. Based on our analysis of the data for this 24-month assessment, the TRIG is recommending no REMS modifications at this time.

12 APPENDICES

12.1 Medical Dictionary for Drug Regulatory Activities (MedDRA) Preferred Terms

Primary SOC	High Level Group	High Level Term	Preferred Term
Overdose			
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Intentional overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Multiple drug overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Multiple drug overdose accidental
Injury, poisoning and procedural complications	Medications errors	Overdoses	Multiple drug overdose intentional
Injury, poisoning and procedural complications	Medication errors	Overdoses	Overdose
Death			
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Accidental death
Nervous system disorders	Neurological disorders NEC	Cortical dysfunction NEC	Brain death
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardiac death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Death
General disorders and administrations site conditions	Fatal outcomes	Death and sudden death	Death neonatal
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden cardiac death
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Sudden death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Agonal death struggle
General disorders and administration site conditions	General system disorders NEC	General signs and symptoms NEC	Apparent death
Social Circumstances	Family Issues	Bereavement issues	Death of companion
Social Circumstances	Family Issues	Bereavement issues	Death of relative
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden unexplained death in epilepsy

Primary SOC	High Level Group	High Level Term	Preferred Term
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Breathing abnormalities	Cardio respiratory arrest
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Breathing abnormalities	Respiratory arrest
Misuse			
General disorders and administration site conditions	Therapeutic and nontherapeutic effects (excl toxicity)	Withdrawal and rebound effects	Medication overuse headache
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Intentional drug misuse
Drug abuse dependence and withdrawal SMQ (Standardized MedDRA Query)			
Abuse			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug abuse
Social circumstances	Lifestyle issues	Drug and chemical abuse	Drug abuser
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Substance abuse
Social circumstances	Lifestyle issues	Drug and chemical abuse	Substance abuser
Social circumstances	Lifestyle issues	Drug and chemical abuse	Ex-drug abuser
Injury, poisoning and procedural complications	Exposures, chemical injuries and poisoning	Poisoning and toxicity	Substance-induced mood disorder
Injury, poisoning and procedural complications	Exposures, chemical injuries and poisoning	Poisoning and toxicity	Substance-induced psychotic disorder
Drug abuse dependence and withdrawal SMQ (Standardized MedDRA Query)			
Inappropriate			
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered at inappropriate site
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Surgical and medical procedures	Therapeutic procedures and supportive care	Therapeutic procedures NEC	Off label use
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered to patient of inappropriate age
Medication Error			
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Intercepted medication error

Primary SOC	High Level Group	High Level Term	Preferred Term
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Intercepted drug prescribing error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Medication error
Injury poisoning and procedural complications	Medication errors	Maladministrations	Counterfeit drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administration error
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug dose omission
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Expired drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dose administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect drug administration duration
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect drug administration rate
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect drug dosage form administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect route of drug administration
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Poor quality drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Underdose
General disorders and administrative sites	Therapeutic and nontherapeutic effects	Therapeutic and nontherapeutic responses	Therapy naive
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Wrong drug administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Wrong technique in drug usage process
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug dispensing error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug label confusion
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug name confusion
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Drug prescribing error
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Incorrect storage of drug
Injury, poisoning and procedural complications	Medication errors	Medication errors NEC	Intercepted drug dispensing error

Primary SOC	High Level Group	High Level Term	Preferred Term
Injury, poisoning and procedural complications	Medication errors	Medication monitoring errors	Labeled drug-disease interaction medication error
Injury, poisoning and procedural complications	Medication errors	Medication monitoring errors	Labeled drug-drug interaction medication error
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered to patient of inappropriate age
Injury, poisoning and procedural complications	Medication errors	Medication errors due to accidental exposures	Accidental drug intake by child
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Multiple use of a single use product
Accidental			
Injury, poisoning and procedural complications	Medication errors	Medication errors due to accidental exposures	Accidental drug intake by child
Injury, poisoning and procedural complications	Medication errors	Medication errors due to accidental exposures	Accidental exposure
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Accidental poisoning
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Toxicity to various agents
Injury, poisoning and procedural complications	Medication errors	Overdoses	Multiple drug overdose accidental
Dependence			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence
Pregnancy, puerperium and perinatal conditions	Foetal complications	Foetal conditions due to maternal conditions	Drug dependence, antepartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, postpartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Polysubstance dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Withdrawal syndrome
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug withdrawal syndrome
Drug Diversion			
Social circumstances	Legal issues	Criminal activity	Drug diversion
Surgical and medical procedures	Therapeutic procedures and supportive care NEC	Therapeutic procedures NEC	Off label use
Respiratory Depression			
Acute central respiratory depression SMQ (Standardized MedDRA Query)			

12.2 AAPCC LISTINGS

The following definitions are used to characterize data in the attached listings of TIRF medicines fentanyl exposures and unknown exposures which were derived AAPCC annual report: Bronstein AC, Spyker DA, Cantilena LR et al. 2010 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th annual report. *Clinical Toxicology*. 2011;49:910-941.

No effect: The patient did not develop any signs or symptoms as a result of the exposure.

Minor effect: The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes (e.g., self-limited gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia without hypotension, and transient cough).

Moderate effect: The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g., corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment).

Major effect: The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).

Death: The patient died as a result of the exposure or as a direct complication of the exposure.

A statement on AAPCC data must be included in all publications referencing AAPCC data. The AAPCC maintains the national database of information logged by the country's 57 poison control centers. Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, an inhalation, or a topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

All data produced from the AAPCCs databases during the year in which the exposures occur is considered preliminary. Changes occur in only a small number of cases each year. This is because it is possible that a poison center may update a case anytime during that year if new data is obtained. In the fall of each year the data for the previous year is locked and no changes are permitted. At that time the data for a year is considered closed.

AAPCC Listing of Exposures to Known TRIG TIRF Immediate-Release Oral Medicines												
Subject	Start Date	Public Case Number	Age (yrs)	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
1	11/4/12 7:52 PM	18482383142012	16	Male	1	1	Aerosol / mist / spray / gas	NULL	Unknown	Fentanyl	Intentional - Abuse	Minor effect
2	12/25/12 8:50 PM	321244603432012	42	Male	2	2	Patch	2	each (e.g. bites / stings)	Fentanyl	Intentional - Unknown	Moderate effect
	12/25/12 8:50 PM	321244603432012	42	Male	1	2	Solid (tablets / capsules / caplets)	90	each (e.g. bites / stings)	Gabapentin	Intentional - Unknown	Moderate effect
3	12/28/12 1:04 AM	21038373392012	23	Female	1	1	Solid (tablets / capsules / caplets)	1600	mcg	Fentanyl	Intentional - Abuse	Minor effect
4	2/11/13 8:49 PM	10165673472013	35	Male	1	1	Unknown	NULL	Unknown	Fentanyl	Unintentional - General	Unable to follow, judged as a potentially toxic exposure
5	2/12/13 12:11 AM	21130043392013	29	Male	1	1	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Misuse	Not followed, minimal clinical effects possible (no more than minor effect possible)
6	3/23/13 10:11 PM	1709933672013	38	Male	1	1	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Major effect
7	3/28/13 10:27 AM	10760983722013	78	Female	3	3	Patch	NULL	Unknown	Fentanyl	Unknown reason	Death
	3/28/13 10:27 AM	10760983722013	78	Female	2	3	Unknown	NULL	Unknown	Hydromorphone	Unknown reason	Death
	3/28/13 10:27 AM	10760983722013	78	Female	1	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Unknown reason	Death
8	3/31/13 1:00 AM	731011543052013	Unknown adult (>=20 yrs)	Female	3	3	Solid (tablets / capsules / caplets)	7	tabs / pills / capsules	Other Antihistamines Alone (Excluding Cough and Cold Preparations)	Intentional - Suspected suicide	Unable to follow, judged as a potentially toxic exposure
	3/31/13 1:00 AM	731011543052013	Unknown adult (>=20 yrs)	Female	1	3	Solid (tablets / capsules / caplets)	8	tabs / pills / capsules	Fentanyl	Intentional - Suspected suicide	Unable to follow, judged as a potentially toxic exposure

AAPCC Listing of Exposures to Known TRIG TIRF Immediate-Release Oral Medicines												
Subject	Start Date	Public Case Number	Age (yrs)	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
	3/31/13 1:00 AM	731011543052013	Unknown adult (>=20 yrs)	Female	2	3	Liquid	3	ounces	Codeine	Intentional - Suspected suicide	Unable to follow, judged as a potentially toxic exposure
9	4/18/13 11:44 PM	18882943192013	24	Male	1	1	Aerosol / mist / spray / gas	NULL	Unknown	Fentanyl	Intentional - Abuse	Major effect
10	5/31/13 7:34 AM	1507423622013	28	Male	2	2	Liquid	NULL	Unknown	Lidocaine	Intentional - Unknown	Major effect
	5/31/13 7:34 AM	1507423622013	28	Male	1	2	Liquid	NULL	Unknown	Fentanyl	Intentional - Unknown	Major effect
11	6/15/13 2:22 AM	18762153532013	31	Male	2	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Oxycodone Alone or in Combination (Excluding Combination Products with Acetaminophen or Acetylsalicylic Acid)	Intentional - Suspected suicide	Moderate effect
	6/15/13 2:22 AM	18762153532013	31	Male	1	4	Patch	3	each (e.g. bites / stings)	Fentanyl	Intentional - Suspected suicide	Moderate effect
	6/15/13 2:22 AM	18762153532013	31	Male	4	4	Unknown	NULL	Unknown	Cocaine	Intentional - Suspected suicide	Moderate effect
	6/15/13 2:22 AM	18762153532013	31	Male	3	4	Unknown	NULL	Unknown	Heroin	Intentional - Suspected suicide	Moderate effect
12	7/15/13 12:40 PM	21416763322013	48	Female	3	4	Liquid	500	mg	Other or Unknown Local and/or Topical Anesthetic	Unintentional - General	Major effect
	7/15/13 12:40 PM	21416763322013	48	Female	1	4	Liquid	160	mg	Fentanyl	Unintentional - General	Major effect
	7/15/13 12:40 PM	21416763322013	48	Female	4	4	Liquid	120	mg	Other Analgesics	Unintentional - General	Major effect
	7/15/13 12:40 PM	21416763322013	48	Female	2	4	Liquid	240	mg	Morphine	Unintentional - General	Major effect
13	7/23/13 3:16 PM	19690023742013	25	Male	1	1	Aerosol / mist / spray / gas	NULL	Unknown	Fentanyl	Intentional - Abuse	Minor effect
14	9/1/13 6:34 AM	4132843842013	23	Female	4	4	Patch	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Moderate effect
	9/1/13 6:34 AM	4132843842013	23	Female	1	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Amitriptyline	Intentional - Suspected suicide	Moderate effect

AAPCC Listing of Exposures to Known TRIG TIRF Immediate-Release Oral Medicines												
Subject	Start Date	Public Case Number	Age (yrs)	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major Category	Reason For Exposure	Medical Outcome
	9/1/13 6:34 AM	4132843842013	23	Female	2	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Suspected suicide	Moderate effect
	9/1/13 6:34 AM	4132843842013	23	Female	3	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Unknown Dietary Supplements or Homeopathic Agents	Intentional - Suspected suicide	Moderate effect
15	9/9/13 7:17 PM	11037533722013	59	Female	1	2	Other	NULL	Unknown	Fentanyl	Unknown reason	Death
	9/9/13 7:17 PM	11037533722013	59	Female	2	2	Patch	NULL	Unknown	Fentanyl	Unknown reason	Death
16	9/13/13 12:23 PM	1688063622013	58	Male	1	1	Liquid	1100	mcg	Fentanyl	Unintentional - Therapeutic error	Moderate effect
17	10/4/13 4:12 PM	732404693602013	41	Female	2	3	Solid (tablets / capsules / caplets)	20	tabs / pills / capsules	Benzodiazepines	Intentional - Suspected suicide	Major effect
	10/4/13 4:12 PM	732404693602013	41	Female	1	3	Unknown	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Major effect
	10/4/13 4:12 PM	732404693602013	41	Female	3	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Trazodone	Intentional - Suspected suicide	Major effect

AAPCC Listing of Exposures to Unknown Fentanyl												
Subject	Start Date	Public Case Number	Age	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major category	Reason For Exposure	Medical Outcome
1	12/4/12 8:54 AM	4448603642012	56	Male	1	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Acetaminophen with Hydrocodone	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	2	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Oxycodone Alone or in Combination (Excluding Combination Products with Acetaminophen or Acetylsalicylic Acid)	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	3	10	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	4	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Pentazocine	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	5	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Short or Intermediate Acting Barbiturates	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	6	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Other Types of Sedative/Hypnotic/ Anti-Anxiety or Anti-Psychotic Drug	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	7	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Amitriptyline	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	8	10	Unknown	NULL	Unknown	Other Dextromethorphan Preparations	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	9	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Propoxyphene	Intentional - Abuse	Death, indirect report
	12/4/12 8:54 AM	4448603642012	56	Male	10	10	Solid (tablets / capsules / caplets)	NULL	Unknown	Diphenhydramine Alone (Unknown if Over the Counter or Prescription)	Intentional - Abuse	Death, indirect report
2	12/4/12 5:53 PM	20593943782012	23	Female	1	2	Solid (tablets / capsules / caplets)	2	tabs / pills / capsules	Acetaminophen with Hydrocodone	Intentional - Abuse	Moderate effect
	12/4/12 5:53 PM	20593943782012	23	Female	2	2	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Abuse	Moderate effect
3	12/5/12 9:28 PM	267253202012	Unknown adult (>=20 yrs)	Male	1	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Oxycodone Alone or in Combination (Excluding Combination Products with Acetaminophen or	Other - Withdrawal	Unable to follow, judged as a potentially toxic exposure

AAPCC Listing of Exposures to Unknown Fentanyl												
Subject	Start Date	Public Case Number	Age	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major category	Reason For Exposure	Medical Outcome
										Acetylsalicylic Acid)		
	12/5/12 9:28 PM	267253202012	Unknown adult (>=20 yrs)	Male	2	3	Unknown	NULL	Unknown	Fentanyl	Other - Withdrawal	Unable to follow, judged as a potentially toxic exposure
	12/5/12 9:28 PM	267253202012	Unknown adult (>=20 yrs)	Male	3	3	Unknown	NULL	Unknown	Other or Unknown Narcotics	Other - Withdrawal	Unable to follow, judged as a potentially toxic exposure
4	1/9/13 12:07 PM	20668103782013	52	Male	1	1	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Abuse	Minor effect
5	1/23/13 12:22 PM	30984613582013	33	Male	1	1	Powder / granules	1	each (e.g. bites / stings)	Fentanyl	Intentional - Abuse	Moderate effect
6	2/11/13 9:20 PM	11442423862013	78	Male	1	1	Other	1	each (e.g. bites / stings)	Fentanyl	Adverse reaction - Drug	Minor effect
7	2/12/13 11:42 PM	5383243332013	42	Male	1	2	Solid (tablets / capsules / caplets)	4	tabs / pills / capsules	Fentanyl	Intentional - Suspected suicide	Unable to follow, judged as a potentially toxic exposure
	2/12/13 11:42 PM	5383243332013	42	Male	2	2	Solid (tablets / capsules / caplets)	14	tabs / pills / capsules	Benzodiazepines	Intentional - Suspected suicide	Unable to follow, judged as a potentially toxic exposure
8	2/17/13 10:10 AM	20754553782013	61	Female	1	1	Other	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Moderate effect
9	2/28/13 8:25 PM	20781363782013	51	Male	1	1	Solid (tablets / capsules / caplets)	1	each (e.g. bites / stings)	Fentanyl	Intentional - Misuse	Moderate effect
10	3/11/13 3:34 PM	4560653642013	31	Female	1	2	Unknown	NULL	Unknown	Fentanyl	Intentional - Abuse	Death, indirect report
	3/11/13 3:34 PM	4560653642013	31	Female	2	2	Unknown	NULL	Unknown	Benzodiazepines	Intentional - Abuse	Death, indirect report
11	3/23/13 6:20 AM	20830413782013	19	Male	1	3	Solid (tablets / capsules / caplets)	12	tabs / pills / capsules	Benzodiazepines	Intentional - Abuse	Moderate effect
	3/23/13 6:20 AM	20830413782013	19	Male	2	3	Liquid	NULL	Unknown	Energy Drinks: Caffeine Only (Without Guarana, Kola Nut, Tea, Yerba Mate,	Intentional - Abuse	Moderate effect

AAPCC Listing of Exposures to Unknown Fentanyl												
Subject	Start Date	Public Case Number	Age	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major category	Reason For Exposure	Medical Outcome
										Cocoa, etc)		
	3/23/13 6:20 AM	20830413782013	19	Male	3	3	Other	2	each (e.g. bites / stings)	Fentanyl	Intentional - Abuse	Moderate effect
12	5/1/13 8:15 PM	20919503782013	37	Male	1	1	Solid (tablets / capsules / caplets)	1	each (e.g. bites / stings)	Fentanyl	Intentional - Abuse	Major effect
13	6/17/13 10:19 PM	21032643782013	Unknown adult (>=20 yrs)	Male	1	1	Other	1	each (e.g. bites / stings)	Fentanyl	Unintentional - General	Unable to follow, judged as a potentially toxic exposure
14	7/22/13 9:44 PM	4094523842013	34	Male	1	1	Other	1	each (e.g. bites / stings)	Fentanyl	Intentional - Abuse	Moderate effect
15	7/31/13 10:54 AM	321711553432013	28	Male	1	2	Other	NULL	Unknown	Fentanyl	Intentional - Abuse	Minor effect
	7/31/13 10:54 AM	321711553432013	28	Male	2	2	Other	NULL	Unknown	Hallucinogenic Amphetamines	Intentional - Abuse	Minor effect
16	8/12/13 7:35 PM	21161483782013	18	Male	1	2	Liquid	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	No effect
	8/12/13 7:35 PM	21161483782013	18	Male	2	2	Solid (tablets / capsules / caplets)	40	mg	Hydromorphone	Intentional - Suspected suicide	No effect
17	8/13/13 1:55 PM	21583013392013	79	Female	1	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Acetaminophen with Oxycodone	Intentional - Suspected suicide	Major effect
	8/13/13 1:55 PM	21583013392013	79	Female	2	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Suspected suicide	Major effect
	8/13/13 1:55 PM	21583013392013	79	Female	3	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Benzodiazepines	Intentional - Suspected suicide	Major effect
	8/13/13 1:55 PM	21583013392013	79	Female	4	4	Solid (tablets / capsules / caplets)	NULL	Unknown	Diphenhydramine Alone (Over the Counter)	Intentional - Suspected suicide	Major effect
18	8/29/13 1:35 PM	321773193432013	54	Female	1	3	Other	2	each (e.g. bites / stings)	Fentanyl	Intentional - Unknown	Major effect
	8/29/13 1:35 PM	321773193432013	54	Female	2	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Acetaminophen with Oxycodone	Intentional - Unknown	Major effect
	8/29/13 1:35 PM	321773193432013	54	Female	3	3	Solid (tablets / capsules / caplets)	NULL	Unknown	Acetaminophen Alone, Adult	Intentional - Unknown	Major effect
18	9/16/13 12:33 PM	321811983432013	54	Female	1	2	Solid (tablets / capsules / caplets)	100	tabs / pills / capsules	Hydromorphone	Intentional - Unknown	Moderate effect
	9/16/13 12:33	321811983432013	54	Female	2	2	Other	1	each (e.g. bites / stings)	Fentanyl	Intentional - Unknown	Moderate effect

AAPCC Listing of Exposures to Unknown Fentanyl												
Subject	Start Date	Public Case Number	Age	Gender	Substance Rank	No of Substances	Formulation	Quantity	Quantity Unit	Major category	Reason For Exposure	Medical Outcome
	PM											
20	10/5/13 3:59 AM	21279543782013	21	Male	1	1	Solid (tablets / capsules / caplets)	NULL	Unknown	Fentanyl	Intentional - Abuse	Moderate effect

12.3 TRIG AERS Safety Surveillance Analysis Report

FDA FAERS Safety Surveillance Analysis Report

FAERS Data Release Date: 2012 Q4

Product: Transmucosal Immediate-Release Fentanyl (TIRF)

Sponsor: TIRF Risk Evaluation Mitigation Strategy (REMS) Industry Group (TRIG) of Companies

Date: 18 December 2013

Status: Final

Version: 1.0

Table of Contents

Overview

The following Quarterly Analysis report was produced from the cumulative 2012 Q4 release of the FDA's Freedom of Information Act (FOIA) FDA Adverse Event Reporting System (FAERS) database which was made publicly available by the FDA in early October, 2013. This Analysis Report focuses on the latest 2 quarters of the AERS data, Q3 and Q4 2012, which are new since the last Quarterly Analysis report was delivered using the Q2 2012 AERS data. As AERS releases are cumulative, the data for both quarters are contained in the most recent Q4 2012 release.

FDA Adverse Event Reporting System (FAERS)

Q4 2012 is the first release of the FDA data using the upgraded FAERS system; prior data releases were produced using the legacy AERS system. There are several notable changes/differences under this new system, including:

- FAERS transitioned from an Individual Safety Report Number based system to a Primary ID based system. Cases are now identified with a PrimaryID, CaseID, and CaseVersion.
- Some fields were removed, including Image ID, Confidential [identity of the reporter], and Death Date
- Serious cases and those with an outcome of death are prioritized for inclusion in the FAERS data
- Drug names for new cases are more standardized

The 2012 Q4 issue of the FAERS data was released approximately six (6) months behind schedule and contains data through December 2012. The FDA has not communicated a plan to release 2013 issues of the FAERS data, which have also been delayed.

MedDRA Version 16.1

The FAERS 2012 Q4 data utilizes MedDRA Version 16.1 for adverse event coding. Therefore, this TRIG FAERS Surveillance analysis also includes an assessment of the TRIG outcomes of interest in order to identify any new Preferred Terms (PTs) of Interest, or existing PTs of interest that may be obsolete under MedDRA 16.1. As a result of this analysis, seven (7) new PTs have been added to the TRIG PTs of interest; 5 PT's have been demoted (rendered obsolete) and cases for these demoted PTs are cross-referenced with existing PTs in MedDRA 16.1.

In total, seventy-four (74) Preferred Terms in MedDRA 16.1 represent a TRIG outcome of interest. Table 20 lists these 74 PTs and also includes a summary of the additions and modifications to the PT list as a result of the upgrade to MedDRA 16.1.

These 74 Preferred Terms of Interest are grouped into the following broad Categories of Interest (TRIG Categories) for aggregate reporting:

- Death

- Overdose (fatal and non-fatal)
- Misuse, abuse, addiction, and diversion
- Inappropriate prescribing
- Medication errors
- Accidental exposure/ingestion

Table 21 lists the PTs associated with each TRIG category above and provides detailed and aggregate results for each category and PT.

Summary of Analysis

The FAERS 2012 Q4 database is comprised of 4,073,790 cumulative case reports, including 232,989 new reports and 115,427 reports from the Q3 2012 quarterly release. Of the cumulative case reports included in this release, seventy-one (71) cases reference a transmucosal immediate-release fentanyl (TIRF) product covered by the FDA Risk Evaluation and Mitigation Strategy (REMS) for TIRF products, with an event date on or after December 28, 2011. Fifty-three (53) of these 71 TIRF product case reports with an event date after December 28, 2011 also specify United States as the Country of Origin and are included in the analysis results described below. Sixteen (16) of these 53 domestic cases are new since the last TRIG Surveillance report was produced using the Q2 2012 release of the AERS data for inclusion in the 12 Month TIRF REMS Assessment Report.

Thirty-four (34) of the 53 domestic cases includeat least one of the TRIG MedDRA Preferred Terms of Interest and are included in the analysis. Eight (8) of these 34 cases with a TRIG MedDRA Preferred Terms of Interest are new since the last TRIG Surveillance Report was produced using the Q2 2012 release of the AERS data for inclusion in the 12 Month TIRF REMS Assessment Report.

In addition, one (1) of the 53 cases that specifies at least one Preferred Term from the MedDRA SMQ (Broad) *Acute Central Respiratory Depression,* is included in this analysis as it contains a possible symptom related to the events included in the TRIG Categories above. The terms included in the SMQ are attached as Appendix 1. None of the individual Preferred Terms from this SMQ is a TRIG Preferred Term of interest; instead counts of reports listing any PT from this SMQ will be summarized into an aggregate count for the entire SMQ and reported separately.

The analysis protocol and assumptions that were used to guide this quarterly analysis are documented in the TRIG AERS Safety Surveillance Plan. This analysis report summarizes the reporting characteristics of the FAERS case reports for TIRF products covered by the shared system REMS. The results are presented in 4 sections as described below.

- **AERS Reports - Cumulative and Quarterly Summary Statistics**: this section provides summary characteristics of the reports comprising the entire AERS database which can be used to provide additional context for interpreting results of the TIRF analysis

- **TIRF Product Reports – Cumulative and Quarterly Summary Statistics**: this section provides the summary report characteristics of case reports which were selected for the TRIG quarterly analysis and that also include a PT or SMQ of interest
- **Outcomes of Interest – Cumulative and Quarterly Summary Statistics:** this section provides counts for each individual Preferred Term of Interest and event categories of Overdose, Death, Abuse, Misuse, Inappropriate Prescribing, Medication Error, Accidental Exposure/Ingestion, Dependence, and Drug Diversion. In addition, counts for the SMQs Drug Abuse, Dependence and Withdrawal, and Acute Central Respiratory Depression are also included.
- **Signal Detection:** This section provides signal detection results for TRIG individual Preferred Terms of interest, for each TRIG event category, and for the 2 SMQ's of interest.

Analysis Results

AERS Reports: Quarterly and Cumulative Summary Statistics

The tables below provide a descriptive summary of the 2012 Q4 FAERS database. These tables include cumulative totals as well as totals for the current (2012 Q4) and prior (2012 Q3) quarter for the overall FAERS database:

- Table 1: Total FAERS Overall Case Report Counts
- Table 2: Figure 1: Total FAERS Gender Summary
- Table 3: Figure 2: Total FAERS Age Summary
- Table 4: Total FAERS Report Type
- Table 5: Total FAERS Initial and Follow up Reports
- Table 6: Total FAERS Outcome Type
- Table 7: Total FAERS Submission Type
- Table 8: Total FAERS Report Source Type
- Table 9: Total FAERS Reporter Occupation
- Table 10: Total FAERS Country of Origin

Table 1 Total FAERS Overall Case Report Counts[1]

Overall Database			
	Cumulative Total	**Current Quarter (Q4 2012)**	**Prior Quarter (Q3 2012)**
Reports	**4,073,790**	**232,989**	**115,427**

[1] From Q4 1997 through December 2012

Table 2 Total FAERS Gender Summary[1]

Gender			
	Cumulative Total	**Current Quarter (Q4 2012)**	**Prior Quarter (Q3 2012)**
Female	2,262,393	131,898	62,408
Male	1,461,344	80,858	38,307
Other/Unknown	350,053	20,233	14,712
Total	**4,073,790**	**232,989**	**115,427**

[1] From Q4 1997 through December 2012

Figure 1 Total FAERS Gender Summary, Current and Prior Quarter

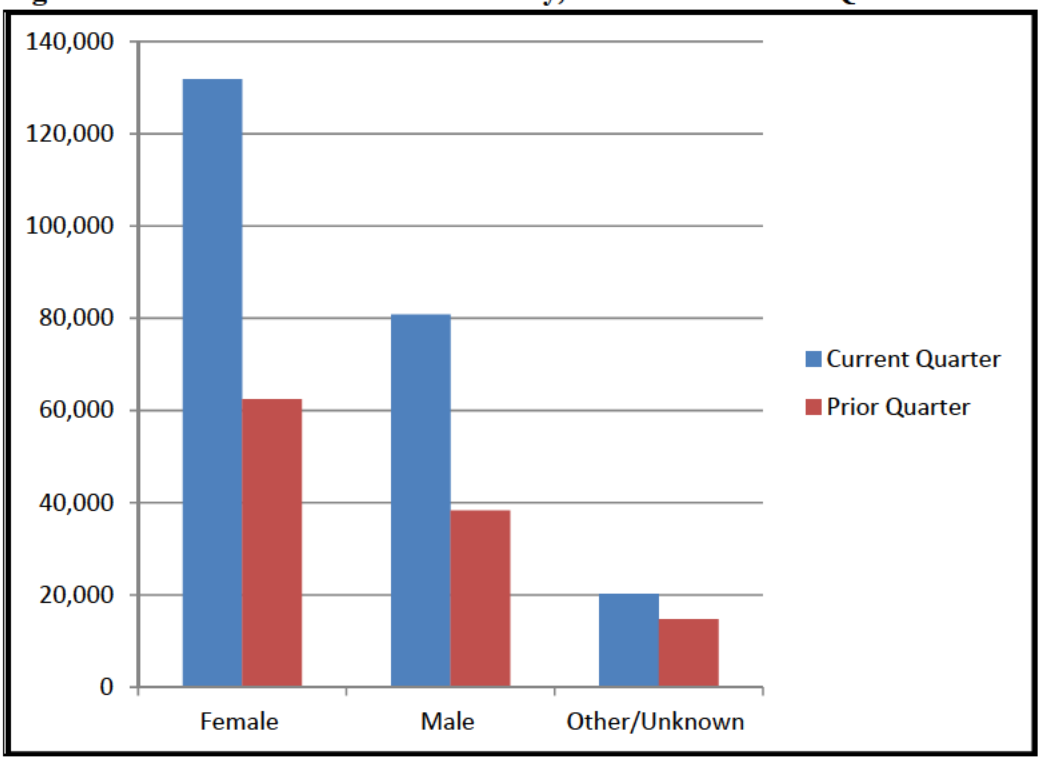


Table 3 Total FAERS Age Summary[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Age 0-2	35,877	1,279	484
Age 3-5	18,702	711	349
Age 6-10	36,362	1,324	624
Age 11-18	87,997	3,666	1,905
Age 19-25	123,593	5,597	3,088
Age 26-35	247,039	11,375	6,257
Age 36-64	1,288,400	68,110	36,143
Age 65+	841,229	40,606	23,258
Age Not Reported	1,394,591	100,321	43,319
Total	**4,073,790**	**232,989**	**115,427**

[1] From Q4 1997 through December 2012

Figure 2 Total FAERS Age Summary, Current and Prior Quarter[1]

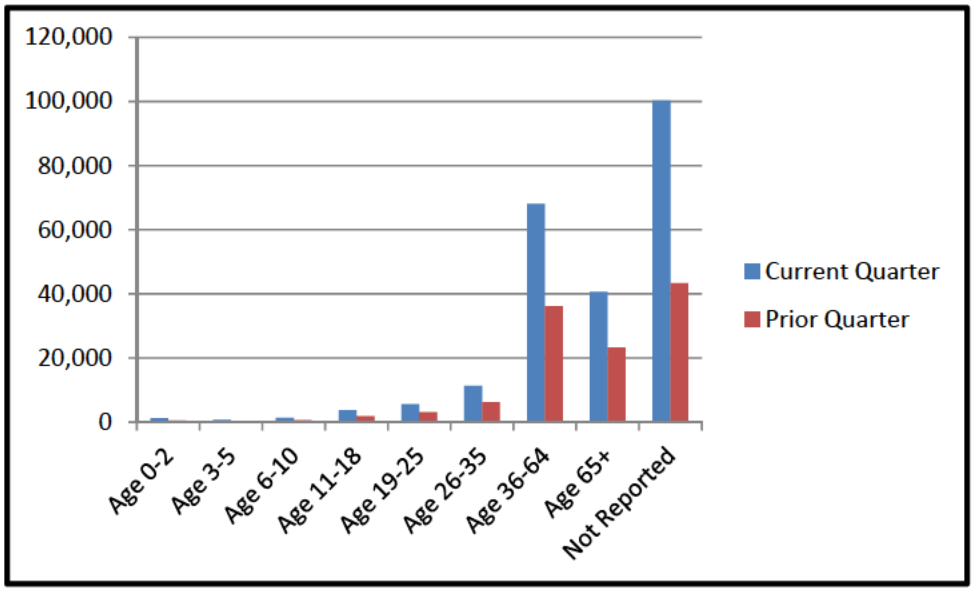


Table4 Total FAERS Report Type[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Direct	338,900	9,476	4,464
Expedited	2,121,933	139,023	68,918
Periodic	1,612,957	84,490	42,045
Total	**4,073,790**	**232,989**	**115,427**

[1] From Q4 1997 through December 2012

Table 5 Total FAERS Initial / Follow-up Reports[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Follow-Up	1,065,536	53,606	37,492
Initial	3,007,986	179,383	77,935
Unspecified	268	-	-
Total	**4,703,790**	**232,989**	**115,427**

[1] From Q4 1997 through December 2012

Table 6 Total FAERS Outcome Type[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Congenital Anomaly	22,354	1,263	796
Death	456,701	37,116	12,066
Disability	138,522	4,980	4,009
Hospitalization	1,141,879	57,250	33,710
Life-Threatening	177,258	6,535	3,589
Required Intervention	121,840	1,231	643
Other	1,479,513	78,481	44,206
Total	**3,538,067**	**186,856**	**99,019**

[1] From Q4 1997 through December 2012

Table 7 Total FAERS Submission Type[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Electronic	2,281,457	212,452	106,478
Other	1,158,176	20,537	8,949
Unspecified	634,157	-	-
Total	**4,073,790**	**232,989**	**115,427**

[1] From Q4 1997 through December 2012

Table 8 Total FAERS Report Source Type*, [1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Foreign	351,770	4,713	1,987
Study	100,467	599	340
Literature	110,871	2,968	1,356
Consumer	605,490	3,677	951
Health Professional	860,114	11,996	3,451
User Facility	3,865	141	16
Company Representative	143,710	871	379
Distributor	11,259	113	15
Other	283,330	32	1,182
Unspecified	2,599,886	217,277	110,960
Total	**5,070,762**	**242,387**	**120,637**

*One report may have zero, one, or multiple report source types
[1] From Q4 1997 through December 2012

Table 9 Total FAERS Reporter Occupation[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
Consumer	1,240,996	103,270	55,151
Lawyer	100,308	3,251	3,612
Other Health Professional	546,345	37,960	19,289
Pharmacist	207,686	9,968	5,186
Physician	894,010	70,153	28,806
Nurse	838	838	-
Sales	2	2	-
Unspecified	1,083,605	7547	3,383
Total	4,073,790	232,989	115,427

[1] From Q4 1997 through December 2012

Table 10 Total FAERS Country of Origin[1]

	Cumulative Total	Current Quarter (Q4 2012)	Prior Quarter (Q3 2012)
United States	2,026,097	160,051	78,472
Unspecified	1,241,744	-	276
Other	805,949	72,938	36,679
Total	**4,073,790**	**232,989**	**115,427**

TIRF Product Reports: Quarterly and Cumulative Summary Statistics

The tables below provide descriptive analyses of thirty-four (34) cumulative FAERS case reports, including eight (8) new reports in this quarter for TIRF products that met the selection criteria as defined in the Quarterly Surveillance Plan and which also contain a TRIG Preferred Term or SMQ of interest. Results are summarized for both the current quarter as well as the cumulative to-date results.

A majority of both the cumulative and new reports containing a PT of interest are for female patients. The new cases are of a slightly older age group (50%, 65+) than that of the cumulative cases (56%, age 36-64; 18%, age 65+). The most common report source of the new cases is a physician (50%), and comparatively, this report source constitutes only 14% of the cumulative TIRF reports to date. Additionally, 75% (n=6) of the new reports and 88.2% (n=30) of the cumulative reports showed the TIRF product as the primary suspect drug. Notably, of the 8 new cases submitted since that last FAERS Surveillance analysis, four (4) reported an outcome of death, representing 50% of outcomes on the newly submitted cases. In 2 of these cases, fentanyl is the drug that is suspected of causing the adverse event whereas it is listed as a concomitant medication in the other 2 cases. Additional characteristics of these 34 reports are further summarized in the following tables:

Table 11 Patient Counts for TIRF Case Reports Containing Events of Interest

Patient Counts	2012 Q2	2012 Q3-Q4	Total to Date
All Reports for TIRF Drugs with event date after 12/28/2011	46*	26	71
US Reports Only	37	16	53
Reports meeting TRIG selection criteria and containing MedDRA Term of Interest	26	8	34
Reports meeting TRIG selection criteria and matching Acute Central Respiratory Depression SMQ	1	0	1

**One case dropped between releases; the event date changed in follow-up report and did not meet TRIG date cutoff*

Table 12 Gender Summary for TIRF Case Reports Containing Events of Interest

Gender	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Males	2	7
Females	6	26
Unknown	0	1

Table 13 Age Summary for TIRF Case Reports Containing Events of Interest

Age	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Age 0-2	0	0
Age 3-5	0	0
Age 6-10	0	0
Age 11-18	0	0
Age 19-25	0	0
Age 26-35	1	2
Age 36-64	3	19
Age 65+	3	5
Unknown Age	1	8

Table 14 Reported Outcomes for TIRF Case Reports Containing Events of Interest*

Outcome	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Congenital Anomaly	0	0
Death	4	4
Disability	0	0
Hospitalization	1	5
Life Threatening	0	0
Requires Intervention	0	0
Other	2	11
Not Specified	1	14

*Cases may have 0, 1 or multiple outcomes specified

Table 15 Submission Type for Case Reports Referencing TIRF products

Submission Type	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Electronic	8	34
Other	0	0
Unspecified	0	0

Table 16 Report Source for TIRF Case Reports Containing Events of Interest

Report Source	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Foreign	0	0
Study	0	0
Literature	0	0
Consumer	0	0
Health Professional	0	0
User Facility	0	0
Company Representative	0	0
Distributor	0	0
Other	0	0
Unspecified	8	34

Table 17 Reporter Occupation for TIRF Case Reports Containing Events of Interest

Reporter Occupation	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Consumer	4	23
Lawyer	0	0
Other Health Professional	0	4
Pharmacist	0	0
Physician	4	5
Unspecified	0	2

Table 18 Role Code for TIRF Products

Role Code	2012 Q3-Q4 N = 8 Reports		Total to date N = 34 Reports	
	N	%	N	%
Primary Suspect	6	75%	30	88.2%
Concomitant	2	25%	4	11.8%

Table 19 Report Type for TIRF Case Reports Containing Events of Interest

Report Type	2012 Q3-Q4 N = 8 Reports	Total to Date N = 34 Reports
Expedited	6	14
Periodic	2	20

Preferred Terms of Interest – Q4 2012 and Cumulative Summary Statistics

The following tables summarize the TRIG Preferred Terms of Interest that were reported on the case reports for TIRF products that met the selection criteria for this analysis.

Each case report may include one or more Preferred Terms. A total of 46 Preferred Terms of Interest for this study are reported across the 34 cumulative case reports selected for TIRF products. **Ten Preferred Terms are reported on the 8 new cases that were submitted since the last AERS Surveillance analysis.** Cumulatively, the most commonly reported Term is "Off label use" (23 cumulative / 5 new) followed by "Drug prescribing error" (8 cumulative / 1 new). Three of the 8 new cases contain the Preferred Term "Death" as one of the reported adverse events, representing 30% of all Preferred Terms of Interest reported on new cases. The tables below summarize the reported terms:

- Table 20: Count of Reported TRIG Preferred Terms of Interest
- Table 21: Count of Reported Preferred Terms by TRIG Category

Table 20 Count of Reported TRIG Preferred Terms of Interest[1]

Unique Preferred Term	2012 Q3-Q4 N = 10 PTs		Total to Date N = 46 PTs		MedDRA 16.1 Version
	N	%	N	%	
Accidental death	0	0.0%	0	0.0%	
Accidental exposure to product by child	0	0.0%	0	0.0%	New PT Obsolete PT: Accidental drug intake by child
Accidental exposure to product	0	0.0%	0	0.0%	New PT Obsolete PT: Accidental exposure

Table 20 Count of Reported TRIG Preferred Terms of Interest[1]

Unique Preferred Term	2012 Q3-Q4 N = 10 PTs		Total to Date N = 46 PTs		MedDRA 16.1 Version
	N	%	N	%	
Accidental overdose	0	0.0%	0	0.0%	Obsolete PT: Multiple Drug Overdose Accidental
Accidental poisoning	0	0.0%	0	0.0%	
Agonal death struggle	0	0.0%	0	0.0%	
Apparent death	0	0.0%	0	0.0%	
Brain death	0	0.0%	0	0.0%	
Cardiac arrest	0	0.0%	0	0.0%	
Cardiac death	0	0.0%	0	0.0%	
Cardio-respiratory arrest	0	0.0%	0	0.0%	
Counterfeit drug administered	0	0.0%	0	0.0%	
Death	3	30.0%	3	6.5%	
Death neonatal	0	0.0%	0	0.0%	
Death of companion	0	0.0%	0	0.0%	
Death of relative	0	0.0%	0	0.0%	
Dependence	0	0.0%	0	0.0%	
Drug abuse	0	0.0%	0	0.0%	
Drug abuser	0	0.0%	0	0.0%	
Drug administered at inappropriate site	0	0.0%	0	0.0%	
Drug administered to patient of inappropriate age	0	0.0%	0	0.0%	
Drug administration error	0	0.0%	1	2.2%	
Drug administration monitoring procedure incorrectly performed	0	0.0%	0	0.0%	New PT
Drug administration monitoring procedure not performed	0	0.0%	0	0.0%	New PT
Drug dependence	1	10.0%	1	2.2%	
Drug dependence, antepartum	0	0.0%	0	0.0%	
Drug dependence, postpartum	0	0.0%	0	0.0%	
Drug dispensing error	0	0.0%	1	2.2%	
Drug diversion	0	0.0%	0	0.0%	
Drug dose omission	0	0.0%	1	2.2%	
Drug label confusion	0	0.0%	0	0.0%	
Drug name confusion	0	0.0%	0	0.0%	
Drug prescribing error	1	10.0%	8	17.4%	
Drug Withdrawal Syndrome	0	0.0%	3	6.5%	
Ex-drug abuser	0	0.0%	0	0.0%	
Expired drug administered	0	0.0%	1	2.2%	
Inappropriate schedule of drug administration	0	0.0%	0	0.0%	

Table 20 Count of Reported TRIG Preferred Terms of Interest[1]

Unique Preferred Term	2012 Q3-Q4 N = 10 PTs		Total to Date N = 46 PTs		MedDRA 16.1 Version
	N	%	N	%	
Incorrect dose administered	0	0.0%	0	0.0%	
Incorrect drug administration duration	0	0.0%	0	0.0%	
Incorrect drug administration rate	0	0.0%	0	0.0%	
Incorrect dosage administered	0	0.0%	0	0.0%	New PT
Incorrect drug dosage form administered	0	0.0%	0	0.0%	
Incorrect route of drug administration	0	0.0%	0	0.0%	
Incorrect storage of drug	0	0.0%	0	0.0%	
Intentional drug misuse	0	0.0%	0	0.0%	
Intentional overdose	0	0.0%	0	0.0%	Obsolete PT: Multiple Drug Overdose Intentional
Intercepted drug dispensing error	0	0.0%	0	0.0%	
Intercepted drug prescribing error	0	0.0%	0	0.0%	
Intercepted medication error	0	0.0%	0	0.0%	
Labeled drug-disease interaction medication error	0	0.0%	0	0.0%	
Labeled drug-drug interaction medication error	0	0.0%	0	0.0%	
Medication error	0	0.0%	0	0.0%	
Medication overuse headache	0	0.0%	0	0.0%	
Multiple use of single-use product	0	0.0%	0	0.0%	
Off label use	5	50.0%	23	50.0%	
Overdose	0	0.0%	0	0.0%	Obsolete PT: Multiple Drug Overdose
Polysubstance dependence	0	0.0%	0	0.0%	
Poor quality drug administered	0	0.0%	0	0.0%	
Prescribed overdose	0	0.0%	0	0.0%	New PT
Prescribed underdose	0	0.0%	0	0.0%	New PT
Respiratory arrest	0	0.0%	0	0.0%	
Substance abuse	0	0.0%	0	0.0%	
Substance abuser	0	0.0%	0	0.0%	
Substance-induced mood disorder	0	0.0%	0	0.0%	
Substance-induced psychotic disorder	0	0.0%	0	0.0%	
Sudden cardiac death	0	0.0%	0	0.0%	
Sudden death	0	0.0%	0	0.0%	
Sudden unexplained death in epilepsy	0	0.0%	0	0.0%	
Therapy naive	0	0.0%	0	0.0%	

Table 20 Count of Reported TRIG Preferred Terms of Interest[1]

Unique Preferred Term	2012 Q3-Q4 N = 10 PTs		Total to Date N = 46 PTs		MedDRA 16.1 Version
	N	%	N	%	
Toxicity to various agents	0	0.0%	0	0.0%	
Underdose	0	0.0%	0	0.0%	
Withdrawal syndrome	0	0.0%	3	6.5%	
Wrong drug administered	0	0.0%	0	0.0%	
Wrong technique in drug usage process	0	0.0%	1	2.2%	
Total PTs reported	**10**	**100.0%**	**46**	**100.0%**	

[1] A report may have one or more PTs

Table 21 Count of Reported Events of Interest Grouped by TRIG Category [1]

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	%	N	%
Overdose	**0**	0.0%	**0**	0.0%
Accidental overdose	0	0.0%	0	0.0%
Intentional overdose	0	0.0%	0	0.0%
Overdose	0	0.0%	0	0.0%
Death	**3**	30.0%	**3**	6.5%
Accidental death	0	0.0%	0	0.0%
Agonal death struggle	0	0.0%	0	0.0%
Apparent death	0	0.0%	0	0.0%
Brain death	0	0.0%	0	0.0%
Cardiac arrest	0	0.0%	0	0.0%
Cardiac death	0	0.0%	0	0.0%
Cardio-respiratory arrest	0	0.0%	0	0.0%
Death	3	30.0%	3	6.5%
Death neonatal	0	0.0%	0	0.0%
Death of companion	0	0.0%	0	0.0%
Death of relative	0	0.0%	0	0.0%
Respiratory arrest	0	0.0%	0	0.0%
Sudden cardiac death	0	0.0%	0	0.0%
Sudden death	0	0.0%	0	0.0%
Sudden unexplained death in epilepsy	0	0.0%	0	0.0%
Misuse	0	0.0%	**0**	0.0%
Intentional Drug Misuse	0	0.0%	0	0.0%
Medication overuse headache	0	0.0%	0	0.0%
Drug abuse dependence and withdrawal SMQ	*1*		7	
Abuse	0	0.0%	**0**	0.0%
Drug abuse	0	0.0%	0	0.0%
Drug abuser	0	0.0%	0	0.0%
Ex-drug abuser	0	0.0%	0	0.0%
Substance abuse	0	0.0%	0	0.0%
Substance abuser	0	0.0%	0	0.0%

Table 21 Count of Reported Events of Interest Grouped by TRIG Category [1]

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	%	N	%
Substance-induced mood disorder	0	0.0%	0	0.0%
Substance-induced psychotic disorder	0	0.0%	0	0.0%
Drug abuse dependence and withdrawal SMQ	*1*		7	
Inappropriate Prescribing	5	50.0%	23	50.0%
Drug administered at inappropriate site	0	0.0%	0	0.0%
Drug administered to patient of inappropriate age	0	0.0%	0	0.0%
Drug administration monitoring procedure incorrectly performed	0	0.0%	0	0.0%
Drug administration monitoring procedure not performed	0	0.0%	0	0.0%
Inappropriate schedule of drug administration	0	0.0%	0	0.0%
Off label use	5	50.0%	23	50.0%
Medication Error	1	10.0%	13	28.3%
Accidental drug intake by child	0	0.0%	0	0.0%
Counterfeit drug administered	0	0.0%	0	0.0%
Drug administered to patient of inappropriate age	0	0.0%	0	0.0%
Drug administration error	0	0.0%	1	2.2%
Drug dispensing error	0	0.0%	1	2.2%
Drug dose omission	0	0.0%	1	2.2%
Drug label confusion	0	0.0%	0	0.0%
Drug name confusion	0	0.0%	0	0.0%
Drug prescribing error	1	10.0%	8	17.4%
Expired drug administered	0	0.0%	1	2.2%
Inappropriate schedule of drug administration	0	0.0%	0	0.0%
Incorrect dose administered	0	0.0%	0	0.0%
Incorrect dosage administered	0	0.0%	0	0.0%
Incorrect drug administration duration	0	0.0%	0	0.0%
Incorrect drug administration rate	0	0.0%	0	0.0%
Incorrect drug dosage form administered	0	0.0%	0	0.0%
Incorrect route of drug administration	0	0.0%	0	0.0%
Incorrect storage of drug	0	0.0%	0	0.0%
Intercepted drug dispensing error	0	0.0%	0	0.0%
Intercepted drug prescribing error	0	0.0%	0	0.0%
Intercepted medication error	0	0.0%	0	0.0%

Table 21 Count of Reported Events of Interest Grouped by TRIG Category [1]

Categories of Interest	Q3-Q4 2012 N = 10 PTs		Total to Date N = 46 PTs	
	N	%	N	%
Labeled drug-disease interaction medication error	0	0.0%	0	0.0%
Labeled drug-drug interaction medication error	0	0.0%	0	0.0%
Medication error	0	0.0%	0	0.0%
Multiple use of single-use product	0	0.0%	0	0.0%
Poor quality drug administered	0	0.0%	0	0.0%
Prescribed overdose	0	0.0%	0	0.0%
Prescribed underdose	0	0.0%	0	0.0%
Therapy naïve	0	0.0%	0	0.0%
Underdose	0	0.0%	0	0.0%
Wrong drug administered	0	0.0%	0	0.0%
Wrong technique in drug usage process	0	0.0%	1	2.2%
Accidental Exposure	0	0.0%	**0**	0.0%
Accidental drug intake by child	0	0.0%	0	0.0%
Accidental exposure to product	0	0.0%	0	0.0%
Accidental overdose	0	0.0%	0	0.0%
Accidental poisoning	0	0.0%	0	0.0%
Toxicity to various agents	0	0.0%	0	0.0%
Dependence	1	10.0%	7	15.2%
Dependence	0	0.0%	0	0.0%
Drug dependence	1	10.0%	1	2.2%
Drug dependence, antepartum	0	0.0%	0	0.0%
Drug dependence, postpartum	0	0.0%	0	0.0%
Drug Withdrawal Syndrome	0	0.0%	3	6.5%
Polysubstance dependence	0	0.0%	0	0.0%
Withdrawal syndrome	0	0.0%	3	6.5%
Drug Diversion	5	50.0%	23	50.0%
Drug diversion	0	0.0%	0	0.0%
Off label use	5	50.0%	23	50.0%
Respiratory Depression	0	N/A	1	N/A
Acute central respiratory depression SMQ	*0*		1	

[1] A report may have more than one PT

Signals of Disproportionate Reporting

Data mining signal detection was carried out for the 53 cumulative TIRF cases selected by TRIG case selection criteria, using the AERS database as the background. In a data mining analysis using a spontaneous reporting database such as AERS, a traditional "denominator" (e.g. the number of patients exposed to a particular drug and/or how long they've been exposed) is not known. To overcome this limitation, data mining methods produce a ratio of disproportionate reporting, comparing the number of reports for a particular Drug / Adverse Event (AE) combination to the number of reports for that AE across all of the other drugs in the AERS database. A disproportionality ratio of 1 indicates that the AE is being reported for the drug of interest at the same rate as it is being reported for all other drugs in the background; a ratio of 2 means that it is being reported at twice the background rate.

There are several commonly used algorithms that produce disproportionality statistics. Three of the most common algorithms were utilized in this analysis. Each of these algorithms also includes a measure of confidence:

- Proportional Reporting Ratio (PRR), Chi Square
- Reporting Ratio (RR), Statistical Unexpectedness (1/P)
- Multi-gamma Poisson shrinker (MGPS), lower bounds of the 95% confidence interval (EB05)

There is no single international standard for signal detection thresholds based on AERS and other spontaneous report databases. The CIOMS VIII Working Group (CIOMS Geneva 2010) dedicates a chapter (VII) to "more complex quantitative signal detection methods", and provides thoughtful perspectives on the role of statistical analysis in the setting of pharmacovigilance. Despite a lack of standards, signaling is commonly defined by the following thresholds:

- PRR: PRR>2, Chi Square >4, and number of reports>3 – considered to be more sensitive but not as specific
- MGPS: EB05>2 (lower bounds of the 95% confidence interval of EBGM) – considered to be more specific, but not as sensitive.
- RR: RR>1, Statistical Unexpectedness (1/P-value) >system calculated, Bonferroni corrected threshold – considered to have intermediate sensitivity / specificity[1]

A Drug / AE combination that crosses a data mining signal threshold is not necessarily indicative that the drug is the cause of that adverse event. For instance, many adverse events that produce high disproportionality scores are related to the reported drug's indication. Therefore, disproportionality results should be interpreted in the context of other information known about

[1] Hochberg AM, Hauben M, Pearson RK, O'Hara DJ, Reisinger SJ, Goldsmith DI, Gould AL, Madigan D., An evaluation of three signal-detection algorithms using a highly inclusive reference event database. Drug Saf. 2009;32(6):509-25. doi: 10.2165/00002018-200932060-00007.

the drug.

Only terms that cross the signaling threshold for at least one of the three data mining algorithms utilized for the analysis are included in the tables below (note that MGPS scores are only calculated when the total number of case reports for the drug and the total number of case reports for the adverse event both exceed one hundred (100), so these scores are not included in the tables below for this quarter). The following tables describe the results of data mining signal detection carried out for the TIRF cases of interest, using the AERS database as the background:

- Table 22 Signals of Disproportionate Reporting, Preferred Terms of Interest
- Table 23 Signals of Disproportionate Reporting, TRIG Categories of Interest
- Table 24 Signals of Disproportionate Reporting, SMQs of Interest

Table 22 Signals of Disproportionate Reporting, Preferred Terms of Interest

Adverse Event	Reports with Drug & Event	Reports with Event	Reporting Ratio	Statistical Unexpectedness	PRR	Chi Square
Off label use	23	17933	98.58	39.46	98.71	2134.53
Drug prescribing error	8	3901	157.63	15.22	157.95	1094.44
Withdrawal syndrome	3	6243	36.94	4.10	36.95	72.14

Table 23 Signals of Disproportionate Reporting, TRIG Categories of Interest

Adverse Event	Reports with Drug & Event	Reports with Event	Reporting Ratio	Statistical Unexpectedness	PRR	Chi Square
Inappropriate prescribing	23	28049	63.03	35.02	63.08	1351.99
Diversion	23	18442	95.86	39.18	95.98	2074.65
Medication error	13	146589	6.82	7.43	6.82	61.03
Dependence	7	44773	12.02	5.72	12.02	60.78

Table 24 Signals of Disproportionate Reporting, SMQ's of Interest

Adverse Event	Reports with Drug & Event	Reports with Event	Reporting Ratio	Statistical Unexpectedness	PRR	Chi Square
Drug abuse, dependence and withdrawal	7	181778	2.96	2.05	2.96	7.57

Relatively robust signals continue to be seen for the Preferred Terms of Interest: "Off label Use" and "Drug prescribing error". A weaker signal was generated for the Preferred Term of Interest "Drug withdrawal syndrome". These are known adverse events for TRIG products. When analyzed according to TRIG Categories of Interest, relatively robust signals were also generated for "Inappropriate use", "Drug diversion", "Medication error", and "Drug dependence". When

examined by MedDRA SMQ, the SMQ “Drug abuse, dependence and withdrawal” generated a somewhat weak signal of disproportionate reporting. These results are similar to those seen in the last quarterly analysis, and no additional signals have appeared.

Appendix 1. Specific Preferred Terms in the Standard MedDRA Query for Acute Central Respiratory Depression

Respiratory Depression
Acute respiratory distress syndrome
Acute respiratory failure
Apnoea
Apnoea neonatal
Apnoeic attack
Bradypnoea
Breath holding
Breath sounds abnormal
Breath sounds absent
Cardio-respiratory distress
Central-alveolar hypoventilation
Hypopnoea
Hypoventilation
Neonatal respiratory depression
Postoperative respiratory failure
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory failure
Respiratory paralysis
Respiratory rate decreased
Severe acute respiratory syndrome
Alveolar oxygen partial pressure abnormal
Alveolar oxygen partial pressure decreased
Anoxia
Asphyxia
Blood gases abnormal
Blood pH abnormal
Blood pH decreased
Capnogram abnormal
Cardiac arrest
Cardiac arrest neonatal
Cardiopulmonary failure
Cardio-respiratory arrest
Cardio-respiratory arrest neonatal
Cheyne-Stokes respiration
Cyanosis
Cyanosis central
Death neonatal
Dyspnoea
End-tidal CO2 abnormal

End-tidal CO2 decreased
Hypercapnia
Hypercapnic coma
Hypoxia
Neonatal anoxia
Neonatal asphyxia
Neonatal hypoxia
Neonatal respiratory acidosis
Neonatal respiratory arrest
Neonatal respiratory distress syndrome
Neonatal respiratory distress syndrome prophylaxis
Orthopnoea
Oxygen saturation abnormal
Oxygen saturation decreased
Oxygen supplementation
PCO2 abnormal
PCO2 decreased
PO2 abnormal
PO2 decreased
Respiration abnormal
Respiratory acidosis
Respiratory disorder
Respiratory disorder neonatal
Respiratory distress
Respiratory fume inhalation disorder
Respiratory gas exchange disorder
Sleep apnoea syndrome
Venous oxygen partial pressure abnormal
Venous oxygen partial pressure decreased
Venous oxygen saturation abnormal
Venous oxygen saturation decreased

12.4 Periodic Stakeholder Surveys

12.4.1 Patient KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Patient Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 2, 24-month REMS Assessment; Version 1.0
Survey Time Period	16 September 2013 to 17 October 2013
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc Galena Biopharma, Inc. Insys Therapeutics Meda Pharmaceuticals Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	18 December 2013

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
ANDA	Abbreviated New Drug Application
CCA	Survey Coordinating Center Associate
CI	Confidence Interval
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Professional
KAB	Knowledge, Attitudes and Behavior
NDA	New Drug Application
PPAF	Patient-Prescriber Agreement Form
PBM	Pharmacy Benefits Manager
REMS	Risk Evaluation and Mitigation Strategy
SCC	Survey Coordinating Center
TIRF	Transmucosal Immediate Release Fentanyl
TIRF Medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
SAP	Survey Analysis Plan
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

1. PATIENT SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt Pharmaceuticals, Mylan, Inc., and Par Pharmaceutical, Inc. At the time of protocol finalization for the Knowledge, Attitude, and Behavior (KAB) surveys, Depomed, Inc. acquired the New Drug Application (NDA) for Lazanda (29 July 2013) from Archimedes Pharma US, Inc., who is no longer a TIRF Sponsor. In addition, Galena Biopharma acquired the NDA for Abstral from ProStrakan Inc., and is now a TIRF Sponsor (as of 01 May 2013) whereupon ProStrakan exited the group. Additionally, Mylan became a TIRF Sponsor on 29 May 2013 due to a pending Abbreviated New Drug Application (ANDA).

The Food and Drug Administration (FDA) has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on 28 December 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the educational materials. The protocol describes the administration of the surveys conducted among patients who are treated with TIRF medicines, or their caregivers.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

This report describes the results from the patient surveys conducted for the 24-month TIRF REMS Access Program Assessment. The 24-month KAB survey launched on 16 September 2013 and closed on 17 October 2013.

2. PATIENT SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines can cause life-threatening breathing problems that can lead to death.
2. Patients should not take TIRF medicines if they are not opioid tolerant.
3. TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4. Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5. Patients should not give TIRF medicines to anyone else even if they have the same symptoms.
6. TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey also includes questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions that were constructed to test patient understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Development

Qualitative research was conducted on a draft of the patient survey prior to implementation of the survey for the 12-month REMS Assessment Report. Qualitative research was not conducted on the survey prior to implementation of the survey for the 24-month REMS Assessment Report.

On 12 March 2013, FDA provided feedback on the 12-month TIRF REMS Access Program Assessment Report that included the recommendation for modification to the patient survey as shown below:

- "For the patient survey, we are concerned that the terms used in question 9 [*For which of the following conditions should I use a TIRF medicine? Headache or migraine pain; Breakthrough pain from cancer; Dental pain; Acute or post-operative pain; Chronic non-cancer pain*] may be too advanced for most patients. Thus for future survey, please conduct the survey using the terms referred to in the Medication Guides. Specifically, please change "acute or postoperative pain" to "pain after surgery," and change "chronic non-cancer pain" to "long-lasting painful conditions not caused by cancer."

The survey was updated and re-submitted to the FDA for review prior to implementation. After this review, on 01 August 2013 FDA provided feedback that included additional recommendations for modification to the patient survey:

- Move the link (page 19) of "*How to learn more about transmucosal immediate release fentanyl medicines*" from the online survey preamble to after respondents complete the survey because the link quoted above may include information that educates or influences a respondent's ability to answer subsequent survey questions.

This change was made to the survey preamble

- Add one question to ask which specific TIRF medicine has the patient taken after Question #3. For example, "*Please specify which TIRF medicine that you or the person you take care of have filled within the last 3 months. (select from a drop-down list of TIRF medicines)(Select all that apply)*".

This questions was added as Q#4 and the responses are shown in Table 2

- Include in analyses all eligible surveys that are completed.

This information was incorporated in the 12-month survey and in all subsequent surveys.

Thus, based on FDA feedback Question 9 was reworded and included in the 24-month survey as Question 10 under "Additional Questions about TIRF Medicines Safety" (Section 5.2.2.1). Besides, the FDA recommended to add one question "Please specify which TIRF medicine that you or the person you take care of have filled within the last 3 months" with a drop-down list from which to make the selection. This was implemented for the 24-month survey as Question 4 (Section 5.1.2, Table 4). The FDA also recommended including in the analyses all eligible surveys that are completed.

3.2 Survey Sample

This survey was conducted among patients who had a prescription filled for a TIRF medicine within the 120 days prior to the survey launch date. A target sample of 300 patients treated with TIRF medicines was to be surveyed in this KAB survey.

The survey was administered using the following modalities:

Self-administered, online through a secure website;

Telephone surveys facilitated by a Survey Coordinating Center Associate (CCA) trained in using a computer-assisted telephone interviewing (CATI) program.

The survey began with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey was expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

3.2.1 Eligibility

Eligibility criteria included patients, 18 years of age or older, and caregivers, 18 years of age or older, who cared for patients who were unable to take the survey for themselves. Respondents (or respondents whose immediate family members) who had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation (UBC), or the FDA were not eligible to participate in this survey.

Respondents who participated in the first wave of the TIRF KAB survey (12-month TIRF REMS Access Program Assessment) were not eligible to participate in subsequent survey waves.

3.2.2 Recruitment

The two methods adopted for recruitment of patients were via a direct letter program and through prescribers who had prescribed TIRF medicines. Patients' invitation letters (Appendix A) informed patients that participants who completed the survey and who provided their contact information would be mailed a $50 gift card to thank them for their participation. The thank you letter included the correct answers to key risk message questions, and a copy of the product-specific Medication Guide.

Recruitment efforts for the 12-month survey had failed to yield the target of 300 completed patient surveys. Therefore, to maximize participation in the 24-month survey, additional recruitment methodology and inclusion criteria were implemented as outlined below:

- The expansion of the network of pharmacies to include a pharmacy network partner and a PBM;

- Recruitment of patients who filled a prescription 120 days prior to survey launch increased from 90 days in the 12-month survey;

- An increased honorarium from $25 to $50; and

- Outbound calls to physician offices to request their support with patient recruitment among their patients who were prescribed a TIRF medicine (Section 3.2.2.2); however, this process did not yield any completed surveys.

Based on the number of prescriptions filled during the 120 days prior to 16 September 2013, the national pharmacy chain network partner and the PBM combined identified all patients filling a prescription and invited all 1903 patients to participate. Of the 347 respondents screened, 302 (87.0%; Table 1 and Table 2) respondents met the eligibility criteria (Section 3.2.1) and completed the survey. It is important to note that once the target of eligible respondents was met, the survey was closed.

3.2.2.1 Direct Letter Program

Subject recruitment was performed via a direct letter program, through a national pharmacy chain network partner and a pharmacy benefits manager (PBM). A sample of patients who had filled a prescription for a TIRF medicine in the 120 days prior to survey implementation were recruited via a letter of invitation sent through the United States Postal Service (USPS). The required number of completed surveys was not achieved within approximately 10 days after the first mailing; therefore, subsequent mailings were sent to non-respondents from the original sample to maximize participation.

3.2.2.2 Physician Recruitment of Patients

Additionally, a random sample of 250 prescribers with at least 5 patients who had filled prescriptions in the 120 days prior to survey implementation were contacted via phone to request their support with patient recruitment. These prescribers were asked to inform their patients who were prescribed a TIRF medicine about the opportunity to participate in the survey by directly handing out or mailing an invitation. Following up on these outbound calls, 204 information packets with patient invitations were mailed to prescribers who expressed willingness to participate in recruiting patients. However, this effort did not result in any completed patient surveys. Prescribers did not receive any compensation for this recruitment effort.

3.3 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the patients' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I don't know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

3.3.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's knowledge that TIRF medicines can cause life-threatening breathing problems.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	***True***

3.3.2 Key Risk Message 2

Key Risk Message 2 refers to the patient's awareness that TIRF medicines should be taken only by opioid-tolerant adult patients.

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
	Please answer True, False, or I don't know for the following statement:	
11	TIRF medicines should only be taken by patients who are opioid tolerant.	***True***
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines.	***True***
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	***False***

3.3.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	***True***
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	***True***
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	***False***

3.3.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's knowledge of the interchangeability of TIRF medicines.

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	***False***

3.3.5 Key Risk Message 5

Key Risk Message 5 refers to the patient's awareness that TIRF medicines should not be given to anyone else even if they have the same symptoms.

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	***False***
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	***True***

3.3.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed.

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	***True***
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	***True***
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	***True***
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	***Get emergency help right away.***

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible patients who completed the survey. Eligible patients were defined as those respondents who answered ***Yes*** to Question 1 (agree to take part in survey), ***Yes*** to Question 2 (filled a prescription for a TIRF medicine in the last 4 months) ***or Yes*** to Question 3 (Caregiver for someone who had filled a prescription for a TIRF medicine in the last 4 months), ***No*** to Question 5 (participated in past survey), ***selected an age group ≥18 years of age*** for Question 6 (patient and caregiver), and ***No*** to Question 8 (worked for a TRIG company, UBC, or FDA).

A completed survey was a survey in which all questions as appropriate were answered. Note that some questions may not have been answered due to skip logic in the survey questionnaire.

4.1.2 Sub-groups of Interest

The following sub-group analyses were conducted if the sub-group included at least 20 respondents.

Sub-group analysis 1: Reading Medication Guide (Question 18, Question 23, and Question 24):

- S-1a - Respondents who got the Medication Guide and read at least most of it
- S-1b - Respondents who did not get a Medication Guide or answered, "I don't know" or who got a Medication Guide and read only some of it or answered, "I don't know."

Sub-group analysis 2: Understanding of Medication Guide (Question 25):

- S-2a - Respondents who understood all of it or most of it
- S-2b - Respondents who understood some of it
- S-2c - Respondents who answered None or "I don't know"
- S-2d - Respondents who answered, "I don't know" to receipt or reading of the Medication Guide.

Sub-group analysis 3: Time to complete survey - Internet:

- S-3a - <10 min
- S-3b - 10 to<20 min
- S-3c - ≥20 min

Sub-group analysis 4: Time to complete survey - Telephone:

- S-4a - <10 min
- S-4b - 10 to <20 min
- S-4c - ≥20 min

Sub-group analysis 5: Modality to complete survey:

- S-5a - Internet
- S-5b – Telephone

Sub-group analysis 6: Highest level of education (Question 37):

- S-6a – Less than, Some, or High school graduate/GED or prefer not to answer
- S-6b - Some college or associate's degree
- S-6c - Bachelor's degree or Master's degree
- S-6d - Professional or Doctoral degree

Sub-group analysis 7: Age group of respondent (Question 6):

- S-7a – 18 to 39
- S-7b – 40 to 49
- S-7c – 50 to 59
- S-7d – 60 or older

Results of sub-group analyses performed are provided in Appendix B, Tables 6.1, 7.1, 7.2, 8.1, 8.2, 9.1, 10.1, 10.2, 11.1, and 11.2. Answers from caregivers and answers from patients will be combined for the sub-group analysis.

4.1.2.1 Primary Analyses

Primary analyses were done for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of each correct response for each individual question/item defined by the key risk message. The correct response to each question/item is included in the body of the risk message table (Section 3.3).

4.1.2.2 Secondary Analyses

Secondary analyses evaluated the number and percentages of correct responses and the average of correct responses within the risk message overall to assess understanding of the comprehensive key risk message. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message.

4.1.3 Patient Report of an Adverse Event, Product Complaint, or Medical Information Request during the Survey

A patient may have reported an adverse event or product complaint while taking the online survey in the free text field of the Internet-based survey. Patients/caregivers who opted for the telephone-based survey may have reported an adverse event or a product complaint while in conversation with the CCA. If the event was mentioned to the CCA, the CCA documented the adverse event or product complaint, the verbatim response, and the respondent's contact information, if provided. The respondent was informed that a representative from the appropriate TIRF medicine manufacturer might contact them to obtain additional information about the adverse event or product complaint. Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or product complaint was forwarded to the appropriate TIRF medicine manufacturer for processing within one business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the patient responses to questions in the KAB survey are summarized in this section, and a full set of responses can be found in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

Patients were recruited through a pharmacy network partner and a PBM, as well as through physician recruitment. Physician recruitment of patients did not result in any completed surveys (Section 3.2.2.2). Based on the number of prescriptions filled during the 120 days prior to survey implementation (16 September 2013), the national pharmacy chain network partner identified 1,450 possible participants and the PBM identified 453 possible participants among patients and caregivers. All of these possible participants were sent a survey invitation letter. A total of 2,454 follow up letters were sent to non-responders (some potential participants received more than one reminder letter). Of the 1,903 possible participants, 347

respondents accessed the survey and were screened for eligibility; 302 of the 347 (87.0%) respondents met eligibility criteria and completed the survey (Table 1); 127 (42.1%) completed the survey by telephone, and 175 (58.0%) completed it on the Internet. From the 302 respondents, 303 surveys were collected. It was identified that one respondent completed the survey twice. Only the first completed survey was included in the analysis for this report.

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Patients/Caregivers N=347[1]	
	All Respondents	
	N	%
Number of invitations issued to patients/caregivers	1903	
Number of reminder letters issued to patients/caregivers	2454	
Number of patients/caregivers screened for participation	347[1]	
Number of patients/caregivers eligible for participation	302	
Number of eligible patient/caregivers eligible for participation	302	
Number of eligible respondents completing the survey	302	87.0[1]
Method of Survey Completion		
Number of surveys completed by telephone	127	42.1[2]
Number of surveys completed by internet	175	58.0[2]

[1] The denominator for the percentages of eligible patients/caregivers is the number of screened patients/caregivers (N=347).

[2] The denominator for percentages completed by telephone or Internet is the number of eligible patients/caregivers who completed the survey (N=302).

Of the 347 respondents, the screening procedure identified 302 eligible participants (including 301 patients and 1 caregiver) all of whom completed the survey (Table 2). Due to the small (n=1) number of caregivers participating in the survey, the majority of results are reported for patients and caregivers combined.

As shown in Table 2, a total of 346 patients/caregivers agreed to participate in this survey. The screening process found 44 (%) respondents were not eligible to participate:

16 (4.6%) respondents were ineligible because they had previously participated in a survey about TIRF medicines; 11 (3.2%) because they did not know if they had previously participated; 15 (4.3%) said "No" when asked if they were caregivers for someone who has filled a prescription for a TIRF medicine within the preceding 4 months; 1 (0.3%) respondent because he/she, or an immediate family member, had worked for a TRIG company in the past, and 1 (0.3%) did not know whether he/she, or an immediate family member, had worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or the FDA in the past and thus were considered ineligible. Thus, there were 302 eligible participants (including one caregiver), all of whom completed the survey (Table 2).

Table 2. Survey Participant Screening Results

Question	Screened Patients/Caregivers N=347		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 1: Do you agree to participate in this survey?				
Yes	346	99.7	302	100.0
No[1]	1	0.3		
Question 2: Within the last 4 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	330	95.1	301	99.7
No	14	4.0	1	0.3
I don't know	2	0.6	0	0.0
Question not asked[2]	1	0.3	0	0.0
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months? As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	1	0.3	1	0.3
No[1]	15	4.3		
I don't know[1]	0	0.0		
Question not asked [2]	331	95.4		

Table 2. Survey Participant Screening Results

Question	Screened Patients/Caregivers N=347		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 5: Have you ever taken part in a survey about a TIRF medicine before?				
Yes[1]	16	4.6		
No	304	87.6	302	100.0
I don't know[1]	11	3.2		
Question not asked [2]	16	4.6		
Question 6: Which of the following groups best describes your age?				
Under 18[1]	0	0.0		
18 – 29	5	1.4	5	1.7
30 – 39	28	8.1	27	8.9
40 – 49	70	20.2	70	23.2
50 – 59	126	36.3	126	41.7
60 – 69	60	17.3	59	19.5
70 or older	15	4.3	15	5.0
Prefer not to answer[1]	0	0.0		
Question not asked[2]	43	12.4		
Question 7: Which of the following groups best describes the patient's age? (Caregivers, only)				
Under 16	0	0.0		
16 – 29	0	0.0	0	0.0
30 – 39	0	0.0	0	0.0
40 – 49	0	0.0	0	0.0
50 – 59	0	0.0	0	0.0
60 – 69	1	0.3	1	0.3
70 or older	0	0.0	0	0.0
Prefer not to answer	0	0.0		
Question not asked[2]	346	99.7		

Table 2. Survey Participant Screening Results

Question	Screened Patients/Caregivers N=347		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]				
Anesta LLC.[1]	0	0.0		
Archimedes Pharma US Inc. [1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) [1]	0	0.0		
Endo Pharmaceuticals Inc. [1]	0	0.0		
Galena Biopharma [1]	0	0.0		
Insys Therapeutics[1]	0	0.0		
Mallinckrodt[1]	0	0.0		
McKesson Specialty Care Solutions[1]	0	0.0		
Meda Pharmaceuticals[1]	0	0.0		
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
RelayHealth[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	0	0.0		
United BioSource Corporation[1]	1	0.3		
FDA[1]	0	0.0		
No[4]	302	87.0	302	100.0
I don't know[1]	1	0.3		
Question not asked[2]	43	12.4		

[1] Ineligible to participate in the survey.
[2] Question not asked due to previous question elimination.
[3] More than 1 response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Of the 302 patient/caregivers, 175 (57.9%) completed the survey online, and 127 (42.1%) completed it by telephone (Table 3). Those taking the survey online took an average of 14.7 minutes to complete it, while those taking it by telephone took an average of 20.1 minutes. Of the 302 participants, 147 (48.7%) online participants required less than 20 minutes to complete the survey, while the other 28 (9.3%) online participants required 20 minutes or more. In the case of telephone participants, 80 (26.5%) required less than 20 minutes and 47 (15.6) took 20 minutes or longer (Table 3).

Table 3. Time to Complete Survey

Time to Complete Survey for Completers (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total[1]**
N	127	175	302
Mean (Standard Deviation)	20.1 (5.20)	14.7 (8.37)	17.0 (7.68)
Minimum	13	6	6
Median	18.6	12.2	16.5
Maximum	44	71	71
Category			
0 – <5 Minutes	0	0	0
5 – <10 Minutes	0	47	47
10 – <15 Minutes	5	70	75
15 – <20 Minutes	75	30	105
20 – <25 Minutes	32	15	47
25 – <30 Minutes	9	6	15
30 Minutes or More	6	7	13

[1] Number of eligible respondents completing the survey (Table 1).

5.1.2 Patient/Caregiver Demographics

The demographic characteristics of respondents who completed the survey are shown in Table 4. The largest number of (n=126; 41.7%) respondents were in the 50 – 59 years age group; 184 (60.9%) were females, and 243 (80.5%) respondents had at least some college or an Associate's degree or higher education. Most prescriptions filled in the 4 months preceding the survey included 117 (38.7%) for Actiq (including generic versions), 107 (35.4%) for Fentora, and 88 (29.1%) for Subsys. Participants were largely from the Northeast (n=113; 37.4%) and South (n=133; 44.0%) regions of the United States (US). There were no

participants from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam identified as "Other" in Table 4.

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months. Please select all that apply.						
Abstral	2	0.7	0	0.0	2	0.7
Actiq, including generic versions of Actiq	117	38.9	0	0.0	117	38.7
Fentora	107	35.5	0	0.0	107	35.4
Lazanda	2	0.7	0	0.0	2	0.7
Onsolis	0	0.0	0	0.0	0	0.0
Subsys	87	28.9	1	100.0	88	29.1
Other	13	4.3	0	0.0	13	4.3
I don't know	2	0.7	0	0.0	2	0.7
Question 6: Which of the following groups best describes your age?						
18 – 29	5	1.7	0	0.0	5	1.7
30 – 39	27	9.0	0	0.0	27	8.9
40 – 49	70	23.3	0	0.0	70	23.2
50 – 59	126	41.9	0	0.0	126	41.7
60 – 69	58	19.3	1	100.0	59	19.5
70 or older	15	5.0	0	0.0	15	5.0
Question 36: What is your gender?						
Male	116	38.5	1	100.0	117	38.7
Female	184	61.1	0	0.0	184	60.9
Prefer not to answer	1	0.3	0	0.0	1	0.3

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 37: What is the highest level of education you have completed?						
Less than high school	2	0.7	0	0.0	2	0.7
Some high school	6	2.0	0	0.0	6	2.0
High School graduate/GED	50	16.6	0	0.0	50	16.6
Some college/Associate's degree	140	46.5	1	100.0	141	46.7
Bachelor's degree	53	17.6	0	0.0	53	17.5
Master's degree	29	9.6	0	0.0	29	9.6
Professional or Doctoral degree	20	6.6	0	0.0	20	6.6
Prefer not to answer	1	0.3	0	0.0	1	0.3
Question 38: What is the main language you speak at home? (Please select only one)						
English	299	99.3	1	100.0	300	99.3
French	0	0.0	0	0.0	0	0.0
Spanish	0	0.0	0	0.0	0	0.0
Portuguese	0	0.0	0	0.0	0	0.0
Italian	0	0.0	0	0.0	0	0.0
German	0	0.0	0	0.0	0	0.0
Chinese	0	0.0	0	0.0	0	0.0
Japanese	0	0.0	0	0.0	0	0.0
Korean	0	0.0	0	0.0	0	0.0
Other	1	0.3	0	0.0	1	0.3
Prefer not to answer	1	0.3	0	0.0	1	0.3
Question 39: Are you Hispanic or Latino?						
Yes	5	1.7	0	0.0	5	1.7
No	290	96.3	1	100.0	291	96.4
Prefer not to answer	6	2.0	0	0.0	6	2.0

Table 4. Demographic Characteristics of Eligible Patients/Caregivers

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 40: For informational purposes only, indicate which of the following U.S. census categories best describes your race?						
American Indian or Alaska Native	5	1.7	0	0.0	5	1.7
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	4	1.3	0	0.0	4	1.3
Black or African American	13	4.3	0	0.0	13	4.3
Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
White	266	88.4	1	100.0	267	88.4
Other	4	1.3	0	0.0	4	1.3
Prefer not to answer	9	3.0	0	0.0	9	3.0
Geographic Distribution (based on Question 40 – State or US Territory)[2]						
Northeast	113	37.5	0	0.0	113	37.4
Midwest	24	8.0	0	0.0	24	7.9
South	132	43.9	1	100.0	133	44.0
West	31	10.3	0	0.0	31	10.3
Other	0	0.0	0	0.0	0	0.0
Prefer not to answer	1	0.3	0	0.0	1	0.3

[1] Number of eligible respondents completing the survey (See Table 1).

[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

5.1.3 TIRF Medicines Education Materials

Respondents were asked about their awareness of educational materials for TIRF medicines, specifically the Medication Guide (Table 5), and the Patient-Prescriber Agreement Form (Table 6).

Of the 302 respondents, 283 (93.7%), reported they had received the Medication Guide for the TIRF medicine prescribed to them; 150 (53.0%) reported receiving the Medication Guide from their doctor with 117 (78.0%) receiving it at the first appointment with the prescribing doctor; 254 (89.8%) respondents received it from their pharmacy; 228 (89.8%) respondents recollected receiving the Medication Guide each time a prescription was filled. Most (n=268; 94.7%) recollected reading the Medication Guide; 170 (63.0%) read all of it with 126 (46.7%) of them understanding all or most (n=125; 46.3%) of the Medication Guide. The respondent also identified that either the pharmacist (n=147; 84.5%) or the prescriber (n=114; 65.5%) offered to explain the Medication Guide.

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 18: Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?						
Yes	282	93.7	1	100.0	283	93.7
No	7	2.3	0	0.0	7	2.3
I don't know	12	4.0	0	0.0	12	4.0
Question 19: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?[2]						
Yes	149	52.8	1	100.0	150	53.0
No	115	40.8	0	0.0	115	40.6
I don't know	18	6.4	0	0.0	18	6.4
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	
Question 20: When was the Medication Guide given to you? [2]						
At the first appointment with the doctor who prescribed the TIRF medicine	116	77.9	1	100.0	117	78.0
At the last appointment with the doctor who prescribed the TIRF medicine	24	16.1	0	0.0	24	16.0
I don't remember	22	14.8	0	0.0	22	14.7

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 19)	152		0		152	
Question 21: Did you receive the Medication Guide from the pharmacy?[2]						
Yes	253	89.7	1	100.0	254	89.8
No	24	8.5	0	0.0	24	8.5
I don't know	5	1.8	0	0.0	5	1.8
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	
Question 22: When was the most recent time that you received a Medication Guide for the TIRF medicine at the pharmacy?[2]						
Only with the first filled prescription	12	4.7	0	0.0	12	4.7
Each time a prescription is filled	227	89.7	1	100.0	228	89.8
Other[3]	6	2.4	0	0.0	6	2.4
I don't know	8	3.2	0	0.0	8	3.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 21)	48		0		48	
Question 23: Did you read the Medication Guide?[2]						
Yes	267	94.7	1	100.0	268	94.7
No	13	4.6	0	0.0	13	4.6
I don't know	2	0.7	0	0.0	2	0.7
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 24: How much did you read? [2]						
All of it	169	62.8	1	100.0	170	63.0
Most of it	78	29.0	0	0.0	78	28.9
Some of it	19	7.1	0	0.0	19	7.0
I don't know	3	1.1	0	0.0	3	1.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 23)	32		0		32	
Question 25: How much of the Medication Guide did you understand?[2]						
All of it	126	46.8	0	0.0	126	46.7
Most of it	124	46.1	1	100.0	125	46.3
Some of it	18	6.7	0	0.0	18	6.7
None of it	1	0.4	0	0.0	1	0.4
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 23)	32		0		32	
Question 26: Did someone offer to explain the Medication Guide to you?[2]						
Yes	173	61.3	1	100.0	174	61.5
No	96	34.0	0	0.0	96	33.9
I don't know	13	4.6	0	0.0	13	4.6
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 27: Who offered to explain the Medication Guide to you? (Select all that apply.)[2]						
The doctor or another healthcare professional in the doctor's office	113	65.3	1	100.0	114	65.5
The pharmacist where the TIRF medicine prescription was filled	146	84.4	1	100.0	147	84.5
Someone else (specify the type of person but not his/her name)[4]	10	5.8	0	0.0	10	5.7
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26)	128		0		128	
Question 28: Did you accept the offer to have the Medication Guide explained to you?[2]						
Yes	110	63.6	1	100.0	111	63.8
No	61	35.3	0	0.0	61	35.1
I don't know	2	1.2	0	0.0	2	1.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26)	128		0		128	
Question 29: How much of the explanation did you understand? [2]						
All of it	81	73.6	0	0.0	81	73.0
Most of it	27	24.5	1	100.0	28	25.2
Some of it	2	1.8	0	0.0	2	1.8
None of it	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Table 5. Responses to Questions About TIRF Medication Guides

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26 or ***No*** or ***I don't know*** to Question 28)	191		0		191	
Question 30: Did you or do you have any questions about the information in the Medication Guide?[2]						
Yes[5]	15	5.3	0	0.0	15	5.3
No	266	94.3	1	100.0	267	94.3
I don't know	1	0.4	0	0.0	1	0.4
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question and thus may not reflect the entire sample because of skip logic in the survey.

[3] Verbatim texts for "Other" selection with regard to the question asking about the most recent time when Medication Guide (Question 22) was received from the pharmacy are presented in Listing 1.

[4] Verbatim texts for other persons offering to explain the Medication Guide (Question 27) are presented in Listing 2.

[5] Questions about the information in the Medication Guide (Question 30) are presented in Listing 3.

The responses to Questions 22, 27 and 30 are listed in Listing 1, Listing 2, and Listing 3, respectively.

5.1.4 Patient-Prescriber Agreement Form

After respondents were asked the questions regarding the key risk messages, they were asked if they had received, read, and understood the PPAF. A total of 223 (73.8%) respondents indicated that someone at the doctor's office had offered to explain the PPAF to them, and that 175 (78.5%) of them understood all of it and 42 (18.8%) understood most of it. The PPAF was signed by 222 (73.5%) respondents; of these 222 responders, 151 (68.0%) reported receiving a copy of the signed PPAF (Table 6).

Table 6. Responses to Questions About the Patient-Prescriber Agreement Form

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	%	n	%	n	%
Question 32: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?						
Yes	222	73.8	1	100.0	223	73.8
No	43	14.3	0	0.0	43	14.2
I don't know	36	12.0	0	0.0	36	11.9
Question 33: How much of the explanation did you understand?[2]						
All of it	174	78.4	1	100.0	175	78.5
Most of it	42	18.9	0	0.0	42	18.8
Some of it	4	1.8	0	0.0	4	1.8
None of it	1	0.5	0	0.0	1	0.4
I don't know	1	0.5	0	0.0	1	0.4
N/A (answered ***No*** or ***I don't know*** to Question 32)	79		0		79	
Question 34: Did you sign a Patient-Prescriber Agreement Form?						
Yes	221	73.4	1	100.0	222	73.5
No	15	5.0	0	0.0	15	5.0
I don't know	65	21.6	0	0.0	65	21.5
Question 35: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?[2]						
Yes	150	67.9	1	100.0	151	68.0
No	38	17.2	0	0.0	38	17.1
I don't know	33	14.9	0	0.0	33	14.9
N/A (answered ***No*** or ***I don't know*** to Question 34)	80		0		80	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

5.2 KAB Survey Objectives

5.2.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total respondent population (patients plus caregivers).

5.2.1.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's knowledge that TIRF medicines can cause life-threatening breathing problems that can lead to death.

Analysis of responses to Question 13d for Key Risk Message 1 showed that 272 (90.1%) of the 302 eligible respondents were aware of the risk of life-threatening breathing problems with TIRF medicines (Table 7).

Table 7. Key Risk Message 1: TIRF Medicines Can Cause Life-Threatening Breathing Problems That Can Lead to Death

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you / the patient.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True[2]	271	90.0 (86.1, 93.2)	1	100.0 (2.5, 100.0)	272	90.1 (86.1, 93.2)
False	0	0.0	0	0.0	0	0.0
I don't know	30	10.0	0	0.0	30	9.9

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

5.2.1.2 Key Risk Message 2

Key Risk Message 2 refers to the respondents' knowledge that they should not take TIRF Medicines if they are not opioid tolerant. Three questions defined this key risk message (Table 8).

In response to the statement in Question 11 that TIRF medicines should only be taken by patients who are opioid tolerant, 277 (91.7%) respondents gave the correct (*True*) response.

The majority (n=267; 88.4%) of respondents understood that opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines (Question 12a). In response to Question 13b, 206 (68.2%) knew that it is not okay for patients to-take TIRF medicines for headache pain, while 75 (24.8%) respondents selected the "I don't know" option. Of the 206 respondents who answered Question 13b (*"It is OK for patients to take TIRF medicines for headache pain)* correctly, 176 respondents had read most of the Medication Guide and 30 respondents had read some or none of it.

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.5 (one-sided 95% CI 2.3, 3.0) out of a possible 3 (Table 8).

Table 8. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True[2]	276	91.7 (88.0, 94.6)	1	100.0 (2.5, 100.0)	277	91.7 (88.0, 94.6)
False	5	1.7	0	0.0	5	1.7
I don't know	20	6.6	0	0.0	20	6.6
Question 12: Please answer True, False, or I don't know for the following statements:						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines.						
True[2]	266	88.4 (84.2, 91.8)	1	100.0 (2.5, 100.0)	267	88.4 (84.3, 91.8)
False	12	4.0	0	0.0	12	4.0
I don't know	23	7.6	0	0.0	23	7.6
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
True	21	7.0	0	0.0	21	7.0
False[2]	205	68.1 (62.5, 73.3)	1	100.0 (2.5, 100.0)	206	68.2 (62.6, 73.4)
I don't know	75	24.9	0	0.0	75	24.8

Table 8. Key Risk Message 2: Patients Should Not Take TIRF Medicines If They Are Not Opioid Tolerant

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Secondary Analyses: Demonstrated Understanding						
0 correct responses	7	2.3	0	0.0	7	2.3
1 correct response	20	6.6	0	0.0	20	6.6
2 correct responses	95	31.6	0	0.0	95	31.5
3 correct responses	179	59.5	1	100.0	180	59.6
Average number of correct responses	2.5	(2.3, 3.0)[4]	3.0	(0.2, 3.0)[4]	2.5	(2.3, 3.0)[4]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider. Three questions define this key risk message (Table 9). In response to Question 12b, 103 (34.1%) respondents understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine while 87 (28.8%) answered incorrectly and 112 (37.1%) selected the "I don't know" option. Of the 103 respondents who gave the correct response, 95 (92.2%) read most of the Medication Guide while 8 (7.8%) read some or none of the Medication Guide. Of the 87 respondents who answered this question incorrectly, 74 (85.1%) had read most of the Medication Guide and of the 112 (37.1%) respondents who selected the "I don't know" response, 79 (70.5%) had read the Medication Guide.

Responding to Question 13c, 301 (99.7%) understood that TIRF medicines should be taken exactly as prescribed by the doctor, and 252 (83.4%) knew that is not all right to take TIRF medicines for short-term pain that will go away in a few days (Question 17b).

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.2 (one-sided 95% CI 2.0, 3.0) out of a possible 3 (Table 9).

Table 9. Key Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True[2]	102	33.9 (28.6, 39.5)	1	100.0 (2.5, 100.0)	103	34.1 (28.8, 39.8)
False	87	28.9	0	0.0	87	28.8
I don't know	112	37.2	0	0.0	112	37.1
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True[2]	300	99.7 (98.2, 100.0)	1	100.0 (2.5, 100.0)	301	99.7 (98.2, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	1	0.3	0	0.0	1	0.3
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you / the patient.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
True	15	5.0	0	0.0	15	5.0
False[2]	251	83.4 (78.7, 87.4)	1	100.0 (2.5, 100.0)	252	83.4 (78.8, 87.5)
I don't know	35	11.6	0	0.0	35	11.6

Table 9. Key Risk Message 3: TIRF Medicines Should Be Taken Exactly As Prescribed By The Healthcare Provider

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding						
0 correct responses	1	0.3	0	0.0	1	0.3
1 correct response	40	13.3	0	0.0	40	13.2
2 correct responses	167	55.5	0	0.0	167	55.3
3 correct responses	93	30.9	1	100.0	94	31.1
Average number of correct responses	2.2	(2.0, 3.0)[4]	3.0	(0.2, 3.0)[4]	2.2	(2.0, 3.0)[4]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's knowledge that they must not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider (Table 10).

Of the 302 respondents, 285 (94.4%) respondents understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

Table 10. Risk Message 4: Patients Should Not Switch From a TIRF Medicine to Another Medicine That Contains Fentanyl Without Talking to a Healthcare Provider

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first						
True	8	2.7	0	0.0	8	2.6
False[2]	284	94.4 (91.1, 96.7)	1	100.0 (2.5, 100.0)	285	94.4 (91.1, 96.7)
I don't know	9	3.0	0	0.0	9	3.0

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.

5.2.1.5 Key Risk Message 5

Key Risk Message 5 refers to patients' knowledge that TIRF medicines should not be given to anyone else even if they have the same symptoms (Table 11).

Response to Question 12d, 296 (98.0%) respondents understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient, and 297 (98.3%) understood that selling or giving away TIRF medicines is against the law (Question 17a).

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 2.0 (one-sided 95% CI 1.8, 2.0) out of a possible 2 (Table 11).

Table 11. Key Risk Message 5: Patients Should Not Give TIRF Medicines to Anyone Else Even if They Have the Same Symptoms

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
True	5	1.7	0	0.0	5	1.7
False[2]	295	98.0 (95.7, 99.3)	1	100.0 (2.5, 100.0)	296	98.0 (95.7, 99.3)
I don't know	1	0.3	0	0.0	1	0.3
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True[2]	296	98.3 (96.2, 99.5)	1	100.0 (2.5, 100.0)	297	98.3 (96.2, 99.5)
False	2	0.7	0	0.0	2	0.7
I don't know	3	1.0	0	0.0	3	1.0
Secondary Analysis: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	11	3.7	0	0.0	11	3.6
2 correct responses	290	96.3	1	100.0	291	96.4
Average number of correct responses	2.0	(1.8, 2.0)[4]	2.0	(-0.3, 2.0)[4]	2.0	(1.8, 2.0)[4]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed (Table 12).

Question 13a elicited the correct (*True*) response from all 302 (100.0%) respondents who were knowledgeable that TIRF medicines should be stored in a safe place out of the reach of children. Of the 302 respondents, 285 (94.4%) understood that TIRF medicines must be disposed of as described in the specific product's Medication Guide (Question 17c). Whereas, most (n=275; 91.1%) respondents understood that a TIRF medicine can cause an overdose and death in any child who takes it (Question 17e); and that they should get emergency help right way (n=264; 87.4%) in response to Question 14 (*What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine?*)

Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.7 (one-sided 95% CI 3.5, 4.0) out of a possible 4 (Table 12).

Table 12. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True[2]	301	100.0 (98.8, 100.0)	1	100.0 (2.5, 100.0)	302	100.0 (98.8, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True[2]	284	94.4 (91.1, 96.7)	1	100.0 (2.5, 100.0)	285	94.4 (91.1, 96.7)
False	0	0.0	0	0.0	0	0.0
I don't know	17	5.6	0	0.0	17	5.6
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True[2]	274	91.0 (87.2, 94.0)	1	100.0 (2.5, 100.0)	275	91.1 (87.3, 94.0)
False	2	0.7	0	0.0	2	0.7
I don't know	25	8.3	0	0.0	25	8.3

Table 12. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed

Question	Patients n=301		Caregivers n=1		Patients & Caregivers N=302[1]	
	n	% (95% CI)[3]	n	% (95% CI)[3]	N	% (95% CI)[3]
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away[2]	263	87.4 (83.1, 90.9)	1	100.0 (2.5, 100.0)	264	87.4 (83.1, 90.9)
Do nothing	17	5.6	0	0.0	17	5.6
Wait an hour and see if the person is OK	2	0.7	0	0.0	2	0.7
I don't know	19	6.3	0	0.0	19	6.3
Secondary Analyses: Demonstrated Understanding						
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	2	0.7	0	0.0	2	0.7
2 correct responses	13	4.3	0	0.0	13	4.3
3 correct responses	50	16.6	0	0.0	50	16.6
4 correct responses	236	78.4	1	100.0	237	78.5
Average number of correct responses	3.7	(3.5, 4.0)[4]	4.0	(0.7, 4.0)[4]	3.7	(3.5, 4.0)[4]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.7 Summary of Understanding of Key Risk Messages

The summary of correct responses to questions detailing the 6 key risk messages is presented in Table 13 below and showed that of the 14 questions, the correct response rates were 70% or higher in respect to 12 of the questions. The correct response rate for Question 13b (*It is OK for patients to take TIRF medicines for headache pain*) was 68.2% and for Question 12b (*If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine*) was 34.1%.

Table 13. Summary of Understanding of Key Risk Messages

Question No.	Question	Desired response	N	% (95% CI)
Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**True**	272	90.1 (86.1, 93.2)
Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.				
11	TIRF medicines should only be taken by patients who are opioid tolerant	**True**	277	91.7 (88.0, 94.6)
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines	**True**	267	88.4 (84.3, 91.8)
13b	It is OK for patients to take TIRF medicines for headache pain	**False**	206	68.2 (62.6, 73.4)
Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.				
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine	**True**	103	34.1 (28.8, 39.8)
13c	TIRF medicines should be taken exactly as prescribed by the doctor	**True**	301	99.7 (98.2, 100.0)
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days	**False**	252	83.4 (78.8, 87.5)
Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.				
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first	**False**	285	94.4 (91.1, 96.7)

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.				
Question No.	**Question**	**Desired response**	**N**	**% (95% CI)**
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient	**False**	296	98.0 (95.7, 99.3)
17a	Selling or giving away TIRF medicines is against the law	**True**	297	98.3 (96.2, 99.5)
Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed				
13a	TIRF medicines should be stored in a safe place out of the reach of children	**True**	302	100.0 (98.8, 100.0)
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide	**True**	285	94.4 (91.1, 96.7)
17e	A TIRF medicine can cause an overdose and death in any child who takes it	**True**	275	91.1 (87.3, 94.0)
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**Get emergency help right away**	264	87.4 (83.1, 90.9)

5.2.2 Other Survey Questions

5.2.2.1 Additional Questions about TIRF Medicines Safety

With the intention of collating responses to survey questions dealing with safety aspects of TIRF medicines and obtain a one-table view, Table 14 was created. The table below summarizes the respondents' answers to some components associated with key risk messages and additional survey questions not associated with key risk messages. These questions assessed whether the patient has been informed of the risks and possible side effects, indications, usage, storage, and the availability of TIRF medicines through the TIRF REMS Access Program.

An HCP from the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine with 259 (85.8%) respondents while 36 (11.9%) respondents did not recall having this conversation.

Most respondents understood that TIRF medicines should not be used for headache or migraine pain (n=234; 77.5%), dental pain (n=264; 87.4%), and pain after surgery (n=207; 68.5%). Only 66 (21.9%) respondents were aware that TIRF medicines are not indicated for long-lasting painful conditions not caused by cancer. Whereas, 194 (64.2%) of the 302 respondents knew that TIRF medicines might be used for breakthrough pain from cancer.

Most (281; 93.0%) respondents recollected that someone in the doctor's office explained the proper way of using the prescribed TIRF medicines while 241 (79.8%) respondents were educated by someone in the doctor's office regarding the proper storage of the prescribed TIRF medicines.

Most (285; 94.4%) respondents were aware of the proper way to dispose of TIRF medicines as described in the product's Medication Guide. However, the awareness that TIRF medicines are only available through the TIRF REMS Access Program scored less than expected with 147 (48.7%) selecting the correct response. Further, most respondents (275; 91.1%) understood that a TIRF medicine might cause overdose and death in any child who takes it.

On an overall basis, the results presented in Table 14 indicate that respondents were aware of most of the precautions needed to ensure safe use of TIRF medicines. Taking into account the percentage of incorrect and "I don't know" responses, patients/caregivers scored somewhat less with regard to the need to stop taking TIRF medicines if the around-the-clock opioid is stopped and the approved indication for TIRF medicines.

Table 14 Responses to All Questions about the Safe Use of TIRF Medicines

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 9: Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.						
Yes	258	85.7	1	100.0	259	85.8
No	36	12.0	0	0.0	36	11.9
I don't know	7	2.3	0	0.0	7	2.3

Table 14 Responses to All Questions about the Safe Use of TIRF Medicines

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 10: For which of the following conditions should I use a TIRF medicine?						
10a: Headache or migraine pain						
Yes	25	8.3	0	0.0	25	8.3
No[2]	233	77.4	1	100.0	234	77.5
I don't know	43	14.3	0	0.0	43	14.2
10b: Breakthrough pain from cancer						
Yes[2]	193	64.1	1	100.0	194	64.2
No	90	29.9	0	0.0	90	29.8
I don't know	18	6.0	0	0.0	18	6.0
10c: Dental pain						
Yes	9	3.0	0	0.0	49	3.0
No[2]	263	87.4	1	100.0	264	87.4
I don't know	29	9.6	0	0.0	29	9.6
10d: Pain after surgery						
Yes	52	17.3	0	0.0	52	17.2
No[2]	206	68.4	1	100.0	207	68.5
I don't know	43	14.3	0	0.0	43	14.2
10e: Long-lasting painful conditions not caused by cancer						
Yes	210	69.8	0	0.0	210	69.5
No [2]	65	21.6	1	100.0	66	21.9
I don't know	26	8.6	0	0.0	26	8.6
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant[3]						
True[2]	276	91.7	1	100.0	277	91.7
False	5	1.7	0	0.0	5	1.7
I don't know	20	6.6	0	0.0	20	6.6

Table 14 Responses to All Questions about the Safe Use of TIRF Medicines

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 12: Please answer True, False, or I don't know for the following statements:						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines[3]						
True[2]	266	88.4	1	100.0	267	88.4
False	12	4.0	0	0.0	12	4.0
I don't know	23	7.6	0	0.0	23	7.6
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine[3]						
True[2]	102	33.9	1	100.0	103	34.1
False	87	28.9	0	0.0	87	28.8
I don't know	112	37.2	0	0.0	112	37.1
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first[3]						
True	48	2.7	0	0.0	8	42.6
False[2]	284	94.4	1	100.0	285	94.4
I don't know	9	3.0	0	0.0	9	3.0
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient[3]						
True	5	1.7	0	0.0	5	1.7
False[2]	295	98.0	1	100.0	296	98.0
I don't know	1	0.3	0	0.0	1	0.3
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children[3]						
True[2]	301	100.0	1	100.0	302	100.0
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Table 14 Responses to All Questions about the Safe Use of TIRF Medicines

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
13b: It is OK for patients to take TIRF medicines for headache pain[3]						
True	21	7.0	0	0.0	21	7.0
False[2]	205	68.1	1	100.0	206	68.2
I don't know	75	24.9	0	0.0	75	24.8
13c: TIRF medicines should be taken exactly as prescribed by the doctor[3]						
True[2]	300	99.7	1	100.0	301	99.7
False	0	0.0	0	0.0	0	0.0
I don't know	1	0.3	0	0.0	1	0.3
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death[3]						
True[2]	271	90.0	1	100.0	272	90.1
False	0	0.0	0	0.0	0	0.0
I don't know	30	10.0	0	0.0	30	9.9
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.) [3]						
Get emergency help right away[2]	263	87.4	1	100.0	264	87.4
Wait an hour and see if the person is OK	17	5.6	0	0.0	17	5.6
Do nothing	2	0.7	0	0.0	2	0.7
I don't know	19	6.3	0	0.0	19	6.3
Question 15: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for?						
Yes	280	93.0	1	100.0	281	93.0
No	19	6.3	0	0.0	19	6.3
I don't know	2	0.7	0	0.0	2	0.7

Table 14 Responses to All Questions about the Safe Use of TIRF Medicines

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 16: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?						
Yes	240	79.7	1	100.0	241	79.8
No	52	17.3	0	0.0	52	17.2
I don't know	9	3.0	0	0.0	9	3.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law[3]						
True[2]	296	98.3	1	100.0	297	98.3
False	2	0.7	0	0.0	2	0.7
I don't know	3	1.0	0	0.0	3	1.0
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days[3]						
True	15	5.0	0	0.0	15	5.0
False[2]	251	83.4	1	100.0	252	83.4
I don't know	35	11.6	0	0.0	35	11.6
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True[2]	284	94.4	1	100.0	285	94.4
False	0	0.0	0	0.0	0	0.0
I don't know	17	5.6	0	0.0	17	5.6
17d: TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).						
True[2]	147	48.8	0	0.0	147	48.7
False	33	11.0	0	0.0	33	10.9
I don't know	121	40.2	1	100.0	122	40.4

Table 14 Responses to All Questions about the Safe Use of TIRF Medicines

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True[2]	274	91.0	1	100.0	275	91.1
False	2	0.7	0	0.0	2	0.7
I don't know	25	8.3	0	0.0	25	8.3

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question

[3] Questions taken from key risk messages

5.2.3 Analyses of Sub-populations

To assess further patients' understanding of key risk messages, sub-group analyses with more than 20 respondents were conducted and outlined in Section 4.1.2. Sub-groups that were not analyzed because they had less than 20 respondents included:

- Sub-group 2b (n=18): Respondents who understood some of the Medication Guide;
- Sub-group Note: The n for sub-group 2c (Respondents who answered "I don't know") was 0; therefore, a column for sub-group 2c was not included in the above Table (n=1): Respondents who answered None or "I don't know") to Question 25 (*How much of the Medication Guide did you understand?*);
- Sub-group 4a (n=0): Time to complete survey (Telephone) <10 minutes.

5.2.3.1 Effectiveness of Medication Guide

The correct response rates for questions detailing the 6 key risk messages are presented in Table 15 by respondents who got the Medication Guide and read at least most of it (sub-group S-1a) and by respondents who did not get a Medication Guide or answered, "I don't know" or who got a Medication Guide and read only some of it or answered "I don't know" (sub-group S-1b).

Of the 248 respondents who read most of the Medication Guide (sub-group S-1a), 234 (94.4%) understood Key Risk Message 1 (*TIRF medicines can cause life-threatening breathing problems that can lead to death*) compared with 38 of the 54 (70.4%) who read some or none of the Medication Guide (sub-group S-1b).

In the case of Key Risk Message 2, 230 (92.7%) respondents who read most of the Medication Guide and 47 (87.0%) of respondents who read some or none of the Medication Guide were

aware that TIRF medicines should only be taken by patients who are opioid tolerant. In addition, 221 (89.1%) respondents who read most of the Medication Guide (sub-group S-1a) and 46 (85.2%) of sub-group S-1b respondents understood the meaning of the term opioid tolerant. Most (n=176; 71.0%) respondents of sub-group S-1a correctly answered that TIRF medicines are not recommended for headache pain compared with 30 of 54 (55.6%) of sub-group S-1b respondents (Table 15).

Of the three questions/statements under Key Risk Message 3, 95 (38.3%) of sub-group S-1a and 8 (14.8%) sub-group S-1b respondents gave the correct response to Question 12b (*If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine*). Almost all (n=247; 99.6%) of sub-group S-1a and 54 (100.0%) of sub-group S-1b respondents correctly identified with the statement that TIRF medicines should be taken exactly as prescribed by the doctor; and 214 (86.3%) of sub-group S-1a and 38 (70.4%) of sub-group S-1b disagreed with the statement that it is okay to take TIRF medicines for short-term pain that will go away in a few days (Table 15).

There was high understanding for Key Risk Message 4 Question 12c (*It is safe to switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider first*) because 233 (94.0%) of sub-group S-1a and 52 (96.3%) of sub-group S-1b responded correctly (Table 15).

Almost all respondents understood Key Risk Message 5 that patients should not give TIRF medicines to anyone else even if they have the same symptoms (Table 15).

Respondents demonstrated a high level of understanding for Key Risk Message 6 that TIRF medicines should be stored in a safe place away from children and properly disposed (Table 15).

Overall, the results indicate that respondents who read all or most of the Medication Guide were better informed regarding the safe use of TIRF medicines. Therefore, the Medication Guide is an effective tool to help patients understand the key risk messages based on the goals of the TIRF REMS. All other sub-group analyses showed that the results are similar to the results in the primary population, and no sub-group-related trends were evident.

Table 15 Correct Responses and Response Rates to Key Risk Message Questions Based on Extent of Reading of Medication Guide

Key Risk Message #	Question	Correct Response Rates			
		Read Most of the Medication Guide N=248		Read Some or None of the Medication Guide N=54	
		N	%	N	%
1	13d: TIRF medicines can cause life-threatening breathing problems that can lead to death	234	94.4	38	70.4
2	11: TIRF medicines should only be taken by patients who are opioid tolerant	230	92.7	47	87.0
	12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines	221	89.1	46	85.2
	13b: It is OK for patients to take TIRF medicines for headache pain	176	71.0	30	55.6
3	12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine	95	38.3	8	14.8
	13c: TIRF medicines should be taken exactly as prescribed by the doctor	247	99.6	54	100.0
	17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days	214	86.3	38	70.4
4	12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first	233	94.0	52	96.3
5	12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient	243	98.0	53	98.1
	17a: Selling or giving away TIRF medicines is against the law	245	98.8	52	96.3

Table 15 Correct Responses and Response Rates to Key Risk Message Questions Based on Extent of Reading of Medication Guide

Key Risk Message #	Question	Correct Response Rates			
		Read Most of the Medication Guide N=248		Read Some or None of the Medication Guide N=54	
		N	%	N	%
6	13a: TIRF medicines should be stored in a safe place out of the reach of children	248	100.0	54	100.0
	17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide	241	97.2	44	81.5
	17e: A TIRF medicine can cause an overdose and death in any child who takes it	230	92.7	45	83.3
	14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? Get emergency help right away	222	89.5	42	77.8

The full set of sub-group analysis tables is provided in Appendix B.

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N=302; Table 1), there were 27 reports of a potential adverse event, product complaint, and/or medical information request associated with the use of TIRF medicines made during survey collection (Appendix B, Listing 4). Respondents who completed the survey online had the option to write in any questions they had in the free-text field. Of the 15 reports made in the free text field of the online survey, nine were requests for medical information related to adverse events, withdrawal, drug administration, and dosage. The remaining six responses were comments that their questions had been answered by the HCP or they had no questions (Appendix B, Listing 3).

6. DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

The specific goal of the TIRF medicines patient KAB survey was to evaluate the level of understanding by patients and caregivers of the risks associated with use of TIRF medicines, the importance of being opioid tolerant before starting a TIRF medicine, strictly following the

directions of the HCP, not switching from one TIRF medicine to another medicine that contains fentanyl without talking to an HCP, the importance of patients not giving TIRF medicines to anyone else even if they have the same symptoms, and storing TIRF medicines in a safe place away from children and proper disposal of unused medicine.

Revisions were made to the 24-month survey based on feedback received from the FDA on the 12-month assessment. Table 16 below shows the changes in key risk message questions between the two survey versions, and the patients' scores in each version. No improvement in correct response rate was noted for Question 10, which was reworded in the 24-month survey in an attempt to improve patient understanding of the question. The one item that scored noticeably lower on the 24-month assessment was the concept that patients should stop taking a TIRF medicine if they stop their around the clock opioid. The TRIG is exploring options to increase awareness of this important safety message, which is discussed in the current PPAF and medication guides for each product. While not a key risk message in the prescriber survey, this concept was also a low scoring item for prescribers even though that it is conveyed in the Prescriber Education Program as a patient counseling message.

Table 16 Correct Response Rate in the 24-Month KAB Survey Compared with the 12-Month KAB Survey in Key Risk Message Questions Modified Between the Two Versions

12-month Survey Question Number	24-month Survey Question Number	Question as Presented in the 24-month Survey	12-month Survey Correct Response (%)	24-month Survey % Correct Response (%)
9	10	For which of the following conditions should I use a TIRF medicine?		
9a	10a	Headache or migraine pain	72.9	77.5
9b	10b	Breakthrough pain from cancer	69.8	64.2
9c	10c	Dental pain	89.6	87.4
9d	10d	Pain after surgery	67.7	68.5
9e	10e	Long-lasting painful conditions not caused by cancer	24.5	21.9
11	12	Please answer True, False, or I don't know for each of the following statements.		
11b	12b	If a patient stops taking around-the clock opioid pain medicine, they must also stop taking the TIRF medicine.	42.7	34.1

The overall higher level of understanding of the remaining items/questions throughout the 6 key risk messages indicates that patients are knowledgeable about the safe use and storage of TIRF medicines. The higher level of understanding in patients who read most or all of the medication guide demonstrates effective communication of the key risk messages, which may also be reinforced by prescribers and pharmacists. The consistent high level of patient understanding of key risk messages between the 12-month and 24-month surveys indicates that the REMS goals are being met with the tools currently in place.

Appendix A Patient Survey Protocol

PROTOCOL TITLE:	**Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Archimedes Pharma US Inc.** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Endo Pharmaceuticals Inc.** **Galena Biopharma** **Insys Therapeutics** **Mallinckrodt** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**6.0**
DATE:	**10 Sep 2013**
APPROVED:	**FINAL**

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LIST OF APPENDICES

FDA_883

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KAB	Knowledge, Attitudes and Behavior
PBM	Pharmacy Benefits Management
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SE/PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics, which are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients

2. Preventing inappropriate conversion between TIRF medicines

3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines, as described in the product-specific Medication Guide. This protocol will describe the administration of the surveys that will be conducted among patients who are treated with TIRF medicines, or their caregivers. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients around the following key information and risk messages communicated through the REMS:

1) TIRF medicines can cause life-threatening breathing problems that can lead to death.

2) Patients should not take TIRF medicines if they are not opioid tolerant.

3) TIRF medicines should be taken exactly as prescribed by the healthcare provider.

4) Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

5) Patients should not give TIRF medicines to anyone else even if they have the same symptoms.

6) TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey will also include questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of patients who have filled a prescription for a TIRF medicine within the past 4 months prior to survey launch and their caregivers. Respondents who have participated in a previous wave of the TIRF REMS KAB survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix B is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

4.1.1 Questions and Statements on REMS Goals

The KAB items of the questionnaire are made up of multiple-choice, closed-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and open-ended questions. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3. The survey is written to follow principles of health literacy and readability.

Questionnaire items will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes," "no," or "I don't know" as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- Questions allowing for the respondent to provide information about when, where and from whom they obtained a Medication Guide, as well as to list questions about information in the Medication Guides.

Questionnaires will be analyzed to determine patient understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, the patient questions, only, are presented in the key risk messages tables. Caregiver questions are presented in Appendix A.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
11	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	**FALSE**

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	**TRUE**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	**TRUE**

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**
13	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**Get emergency help right away.**

4.1.2 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and PPAF will be asked after the key risk message questions, and will be followed by the collection of demographic information at the completion of the survey.

4.2 Subject Recruitment

Patients will be recruited through a direct letter program. Patients will be invited through a network of national pharmacies and a pharmacy benefits management (PBM) partner, which

each have broad demographic coverage and include patients in 49 states. Leveraging one or more of these partners, a list will be created of patients who have filled a prescription for a TIRF medicine within 4 months prior to survey launch (first prescriptions and refills). Patients in this list will be invited to participate in the survey through an invitation letter (Appendix B) mailed directly to the patients on the pharmacy or PBM's letterhead at the corporate level via the United States (US) Postal Service.

Additionally, outbound calls will be placed to prescribers to ask for their support in informing patients about the opportunity to participate in the survey by providing an invitation directly to patients who are prescribed a TIRF medicine. A random sample of up to 250 prescribers with at least 5 patients who have filled prescriptions in the 4 months prior to survey implementation will be contacted for this purpose. If a prescriber expresses willingness to support the survey effort, an information packet including invitation letters will be mailed to the prescriber. Prescribers will not receive any compensation for this support.

The invitation will indicate that participants will receive a $50 gift card for completing the survey. Each invitation will also include a unique code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. The unique code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.

A random sample of patients who have filled a prescription for a TIRF medicine within the 4 months prior to survey launch will be chosen from the pharmacy partner's or PBM database. This sampling approach will be used to create several batches of survey invitations. The overall number of unique patients and the duration of the survey period will dictate the size and number of invitation batches. If the required number of completed surveys is not achieved within a reasonable time frame, a second mailing will be sent to non-respondents from the original batch mailing and initial invitations will be sent to patients in the second batch. If the required number of completed surveys is still not achieved within a reasonable time frame, reminder letters will be sent to the patients in the second batch and initial invitations will be sent to the third batch of patients. If these efforts do not result in the required number of surveys within a reasonable time frame, then a new random sample of patients may be selected. The intervals for sending reminder invitations to non-responders and for selecting a new sample will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

All respondents who complete the survey and who provide their contact information will be mailed a $50 gift card to thank them for their participation. The mailing will include a thank you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating patients will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of patients for participation.

Respondents will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 patients treated with TIRF medicines is proposed for the survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each key risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

The following respondents are eligible to participate in the survey:

- Patients who are 18 years of age or older who have filled a prescription for at least one of the TIRF medicines within 4 months prior to survey launch
- Caregivers 18 years of age or older who care for patients who have filled a TIRF medicine prescription within the past 4 months prior to survey launch and are unable to take the survey for themselves

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Patients who have previously participated in the TIRF REMS KAB survey (this exclusion applies to the second and subsequent waves only)
- Patients or their immediate family members who have ever worked for Anesta LLC, Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; ProStrakan Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm patient eligibility. The entire survey is expected to take approximately 20 minutes to complete. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, respondents are immediately notified with a thank you message that survey participation has ended. If eligible, respondents are allowed to continue survey participation.

The electronic data capture (EDC) system that is used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient-identifying information will be stored separately from survey data.

6.1.1 Telephone

The telephone survey is facilitated by a trained interviewer from the Survey Coordinating Center using a CATI program. The respondent will be required to provide a unique code to access the survey. Working from a CATI script, the interviewer will read questions or statements to the respondent and enter the responses into the EDC system. Screening and main

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elements of the questionnaire will be administered sequentially during the same telephone call. Telephone interviewing allows participation of respondents who do not have Internet access, or prefer to complete the survey in this manner.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If respondents select to participate in the survey online, they will be directed to a secured website and instructed to enter a unique code to access the survey. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer interviews.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. Any free text fields will be grouped into applicable categories. Verbatim text from open-ended questions will be displayed when appropriate. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed all questions presented to them
- Description of survey participants, including:
  - Type of respondent (patient/caregiver)

  - Age (patient/caregiver)
  - Gender (respondent)
  - Educational level (respondent)
  - Main language spoken at home (respondent)
  - Ethnicity (respondent)
  - Race (respondent)
  - Geographic region (respondent)

- Data from all respondents who completed all questions presented to them in the survey ("completers") will be analyzed, including:
  - Frequency distribution of responses to each key risk message question.
  - Percent of completers selecting desired response to each question relating to each key risk message and 95% CI.

Measurement of understanding will be computed for each question of the key risk message individually. A secondary analysis will be conducted to determine the number of completers who answered all items correctly for the key risk message. Behavior questions will be summarized on a question-by-question basis and are not included in the analysis by key risk message.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The survey will be conducted via the Internet and by telephone. It is possible that a respondent may report an adverse event or other safety event experienced while taking TIRF medicines either in free text fields of the survey or while in conversation with the Survey Coordinating Center. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. The respondent will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact him/her if there are questions about the survey. The Internet-based questionnaires will be monitored for any comments recorded in free text fields. Information on all comments that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE/PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE/PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail a $50 gift card, a Thank You Letter, a product-specific Medication Guide, and correct survey responses to key risk message questions after the survey is completed. Respondent contact information is also requested in the event a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information. A respondent may be contacted only if clarification or follow-up is needed regarding a possible safety event that was mentioned to the interviewer or recorded in free text fields of the online survey.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to receive TIRF medicines.

This protocol and survey will be reviewed and approved by a central Institutional Review Board (IRB) before administration of the survey.

APPENDIX A Screening and Main Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets. **[PATIENT]** indicates text applicable to a patient when it differs from survey text for caregivers, parents and legal guardians. **[PARENT/CAREGIVER/LEGAL GUARDIAN]** indicates text applicable to parents, caregivers, and legal guardians when it differs from survey text for patients.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by tlelphone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as “I don’t know,” “Prefer not to answer” or “None of the above” will always appear at the end of the randomized responses.

- **[GO TO Ax]** (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

Survey Legend

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

  Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

  Northeast Region
  - New England Division - ME, NH, VT, MA, RI, CT
  - Middle Atlantic Division - NY, NJ, PA

  Midwest Region
  - East North Central Division - OH, IN, IL, MI, WI
  - West North Central Division - MN, IA, MO, ND, SD, NE, KS

  South Region
  - South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
  - East South Central Division - KY, TN, AL, MS
  - West South Central Division - AR, LA, OK, TX

Survey Legend

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are **T**ransmucosal **I**mmediate **R**elease **F**entanyl medicines, also known as rapid onset opioids (and sometimes called "fast acting fentanyls") or TIRF medicines.

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB). Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

How to Learn More About This Survey

If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297.

Once you have answered a question and moved on, you cannot go back and change your answers.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4). Be sure to write down this telephone number; it will not be displayed again.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are Transmucosal Immediate Release Fentanyl medicines, also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** (and sometimes called "fast acting fentanyls") or TIRF medicines.

(INTERVIEWER: Pronounce "TIRF," then spell out T-I-R-F).

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

Now I would like to tell you about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

Now I would like to tell you about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB). Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

Please feel free to ask me to repeat any questions or statements as we go through the survey.

Once you have answered a question and moved on, you cannot go back and change your answers.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4).

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 4 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.

   - ○ Yes **[GO TO Q4]**
   - ○ No
   - ○ I don't know

3. Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months? As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands.

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. **[PATIENT]** For which TIRF medicines have you filled a prescription in the last 4 months? Please select all that apply.

[CAREGIVER] For which TIRF medicines has the person you care for filled a prescription in the last 4 months? Please select all that apply.

- □ Abstral
- □ Actiq, including generic versions of Actiq
- □ Fentora
- □ Lazanda
- □ Onsolis
- □ Subsys
- □ Other
- ○ I don't know **[CLEAR ALL OTHER SELECTIONS]**

5. Have you ever taken part in a survey about a TIRF medicine before?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

6. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE]**
- ○ 18 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

7. **[CAREGIVER ONLY]** Which of the following groups best describes the patient's age?

- ○ Under 16
- ○ 16 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer

8. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- ☐ Anesta LLC **[TERMINATE]**
- ☐ Archimedes Pharma US Inc. **[TERMINATE]**
- ☐ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
- ☐ Endo Pharmaceuticals Inc. **[TERMINATE]**
- ☐ Galena Biopharma **[TERMINATE]**
- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ ProStrakan, Inc. **[TERMINATE]**
- ☐ RelayHealth**[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA (Food and Drug Administration) **[TERMINATE]**
- ☐ No **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**

[PREAMBLE 2]

[PATIENT]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for you. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

Please think of the information that you read or that was provided to you by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[CAREGIVER]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for the patient. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you or to the patient by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

9. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

   [CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed to the patient? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

   - ○ Yes
   - ○ No
   - ○ I don't know

10. **[PATIENT]** For which of the following conditions should I use a TIRF medicine?

    [CAREGIVER] For which of the following conditions should the person I take care of use a TIRF medicine?

	[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
10a.	Headache or migraine pain	○	○	○
10b.	Breakthrough pain from cancer	○	○	○
10c.	Dental pain	○	○	○
10d.	Pain after surgery	○	○	○
10e.	Long-lasting painful conditions not caused by cancer	○	○	○

11. Please answer True, False, or I don't know for the following statement:

TIRF medicines should only be taken by patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

12. Please answer True, False, or I don't know for each of the following statements.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
12a. Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	○	○	○
12b. If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	○	○	○
12c. It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	○	○	○
12d. A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	○	○	○

13. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
13a.	TIRF medicines should be stored in a safe place out of the reach of children.	○	○	○
13b.	It is OK for patients to take TIRF medicines for headache pain.	○	○	○
13c.	TIRF medicines should be taken exactly as prescribed by the doctor.	○	○	○
13d.	TIRF medicines can cause life-threatening breathing problems that can lead to death.	○	○	○

14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- ○ Wait an hour and see if the person is OK.
- ○ Get emergency help right away.
- ○ Do nothing.
- ○ I don't know

15. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

16. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

17. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
17a. Selling or giving away TIRF medicines is against the law.	○	○	○
17b. It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
17c. TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
17d. TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).	○	○	○
17e. A TIRF medicine can cause an overdose and death in any child who takes it.	○	○	○

[PREAMBLE 3]

[PATIENT] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for the patient.

[BOTH] A Medication Guide is a paper handout that contains important information about the risks associated with the use of a TIRF medicine and how to use it safely. Medication Guides always include the title "Medication Guide" followed by the name of the medicine and its pronunciation. The Medication Guide usually has a section titled "What is the most important information I should know?" The Medication Guide is in a question-and-answer format and may be given to you by your pharmacist or doctor.

[END PREAMBLE 3]

18. **[PATIENT]** Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?

[CAREGIVER] Have you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for the patient?

- ○ Yes
- ○ No **[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

19. **[PATIENT]** Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

[CAREGIVER] Did you or the patient receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

- ○ Yes
- ○ No **[GO TO Q21]**
- ○ I don't know **[GO TO Q21]**

20. **[PATIENT]** When was the Medication Guide given to you? Please select all that apply.

[CAREGIVER] When was the Medication Guide given to you or the patient? Please select all that apply.

- ○ At the first appointment with the doctor who prescribed the TIRF medicine
- ○ At the last appointment with the doctor who prescribed the TIRF medicine
- ○ I don't remember **[CLEAR ALL OTHER SELECTIONS]**

21. **[PATIENT]** Did you receive the Medication Guide for the TIRF medicine from the pharmacy?

[CAREGIVER] Did you or the patient receive the Medication Guide for the TIRF medicine from the pharmacy?

- ○ Yes
- ○ No **[GO TO Q23]**
- ○ I don't know **[GO TO Q23]**

22. **[PATIENT]** How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] How frequently do you or the patient receive a Medication Guide for the TIRF medicine at the pharmacy?

- ○ Only with the first filled prescription
- ○ Each time a prescription is filled
- ○ Other (please specify): _____
- ○ I don't know

23. Did you read the Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]**
- ○ I don't know **[GO TO Q26]**

24. How much did you read?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ I don't know

25. How much of the Medication Guide did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

26. Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

27. Who offered to explain the Medication Guide to you? (Select all that apply.)

- □ The doctor or another healthcare professional in the doctor's office
- □ The pharmacist where the TIRF medicine prescription was filled
- □ Someone else (specify the type of person but not his/her name)

_____

28. Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

29. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

30. Did you or do you have any questions about the information in the Medication Guide?

- ○ Yes
- ○ No **[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

31. What are your questions? **[MULTILINE INPUT]**

[PREAMBLE 4]

The next set of questions is about the Patient-Prescriber Agreement Form for TIRF medicines. As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands. The Patient-Prescriber Agreement is a form that is signed by the doctor and the patient or their caregiver. This form may also be referred to as the Prescriber-Patient Agreement.

[END PREAMBLE 4]

32. Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- ○ Yes
- ○ No **[GO TO Q34]**
- ○ I don't know **[GO TO Q34]**

33. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

34. **[PATIENT]** Did you sign a Patient-Prescriber Agreement Form?

[CAREGIVER] Did you or the person you are caring for sign a Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

35. Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

36. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

37. What is the highest level of education you have completed?

- ○ Less than high school
- ○ Some high school
- ○ High school graduate/GED
- ○ Some college/Associate's degree
- ○ Bachelor's degree
- ○ Master's degree
- ○ Professional or Doctoral degree
- ○ Prefer not to answer

38. What is the main language you speak at home? (Please select only one.)

- ○ English
- ○ French
- ○ Spanish
- ○ Portuguese
- ○ Italian
- ○ German
- ○ Chinese
- ○ Japanese
- ○ Korean
- ○ Other
- ○ Prefer not to answer

39. Are you Hispanic or Latino?

- ○ Yes
- ○ No
- ○ Prefer not to answer

40. For informational purposes only, which of the following U.S. census categories best describes your race? (Please select only one.)

- ○ American Indian or Alaska Native
- ○ Asian (origins of Far East, Southeast Asia or the Indian subcontinent)
- ○ Black or African American
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ Other
- ○ Prefer not to answer

41. In which state do you live?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

You are eligible to receive a $50 gift card for your time completing the survey. In order to receive the gift card, we need to collect your name and address so that we can mail it to you. If you do not provide your name and address you will not receive the gift card for your time taking the survey.

42. Do you agree to give us your name and mailing address so we can send your payment?

- ○ Yes
- ○ No **[SKIP TO CLOSING 2]**

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

43. Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[CLOSING 3]

This is the end of the survey. If you have questions about the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Thank you again for your help.

[END OF SURVEY CONTENT]

APPENDIX B Patient Letter of Invitation

[PAT_FIRST_NAME] [PAT_LAST_NAME
[CURR_DATE]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

Thank you for choosing [pharmacy partner or PBM name] for your prescription needs. The purpose of this letter is to inform you about a voluntary research survey being conducted by [COMPANY], the maker of [BRAND_GENERIC]. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about [BRAND] and other medicines like it. The first 300 people who complete this 20-minute survey and provide their contact information will receive a $50 [pharmacy partner or PBM name] gift card from [COMPANY] to thank them for their time.

You may be eligible to take part if you have taken [BRAND] and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about [BRAND] and where you get your medical information.

If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

It is recommended that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

(over, please)

You are not required to take part in this survey. If you choose to take part, please be assured that your contact information and your individual responses will be kept strictly confidential. You will not be asked to identify yourself to participate in the survey. However, if you wish to receive the $50 gift card from [COMPANY], you must provide your name and contact information for delivery. Your answers to the survey questions will be combined with answers given by others, and your name will not be used in any written report or publication. Neither taking the survey nor your answers to the questions will affect your ability to receive or take [BRAND].

Sincerely,

[Pharmacy partner or PBM name]

[COMPANY] funded the cost of the gift card, the cost of mailing this letter and paid a fee to [pharmacy partner or PBM name]. The research study is not being conducted by [pharmacy partner or PBM name]. No information that can identify you, your medication, or your health condition will be provided by [pharmacy partner or PBM name] to [COMPANY]. This letter provides information about a drug prescribed by your doctor and is not a recommendation by [pharmacy partner or PBM name] to use a particular drug for your condition. Call [pharmacy partner or PBM name] toll free at xxx-xxx-xxxx if you do not wish to continue receiving mailings about [BRAND] from [pharmacy partner or PBM name].

Appendix B Patient Survey Listings and Sub-group Analyses Tables

Listing 1 VERBATIM RESPONSES TO QUESTION 22 (How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?)

Verbatim Response
not all the time
7- 8 times year
Yearly or dosage change
Every 3 months.
There is one in each box
received in the mail
I have only filled 1 perscription

Listing 2 VERBATIM RESPONSES TO QUESTION 27 (Other person offering explanation of the Medication Guide)

Verbatim Response
drug rep
Husband
manufacturer on the phone
My husband is a Pharmacist
my mom she is a nurse.
Nurse Practitioner in Doctors Office
son in law who is a doctor and daughter is rn
Subsys drug Rep
the manufacturer's rep
Wife

Listing 3 VERBATIM RESPONSES TO QUESTION 30 (Questions about the information in the Medication Guide)

Verbatim Response
Allergic reactions and safety instructions
are there withdrawal symptoms?
how to get off in a safe manner
I asked questions about going off of the medication and was it safe to only use 1 one day and the max I am prescribed (4) a day
I don't remember at this point, I would have to reread the medication guide to be able to answer this question with my questions that I have.
I wondered over time, will it rot me teeth?
In the guide it has section that has long term side effects it has dental. It does not explain the dental.
my one question was on how long it should take a Actiq to dissolve in your mouth
My questions have been subsequently worked out with my prescribing healthcare officials.
My questions were answered by the doctor after I read the Guide. Safety, and how it would affect me with relation to the other pain meds I am taking.
None
sorry,,,I answered incorrectly, I had a question in regard to my fentanyl patch.. the med guide said not to sunbathe...and I was wondering how the transdermal patch would be effected by the sun or heat from the sun
the questions were answered by the doctor
Was it possible to only spray half of the container?
What happens if I can't dissolve the medicine in 20min? If the first sucker doesn't not relieve the pain how soon can I take the second one?

Listing 4 REPORTED ADVERSE EVENTS, PRODUCT COMPLAINTS, or Requests for Medical Information

Verbatim Response
"I'm Sorry. I'm just getting over a cold."
"Sometimes I break out from the lollipop, is there latex in it?"
"What I have had is 5 back fusions, 3 Lumbar and 2 Cervical. I have nerve damage in my back. I can only take Fentanyl cause I am allergic to everything else."
Bigger print I can hardly read it. It is too complicated.
Could I say something to pass on to the people who made these drugs? They are too damn expensive. Even the generic is too expensive. And now I won't even be able to get these suckers anymore because the FDA won't let you have them unless you have cancer. I got flagged at the pharmacy and they called my doctor. When they found out that they were for pain after my truck accident they told my doctor that he couldn't prescribe it for me anymore. This is my last month. These things worked great for me and I don't know what I'm going to do now.
For me, I am not using for cancer pain. I am using for long term pain relief.
I broke my left leg. I broke my tibia in 5 places on July 15th. When I took the SUBSYS the medicine worked immediatley. It took the pain from about a 12 to a 2. Especially in a broke leg I feel like it's a good product especially for a broke leg. It helped get me through the first few weeks.
I do take the medication for long term pain but it is not because of cancer.
I dont take it for cancer pain. I'm opioid tolerant.
I had surgery for spinal stenous spinal stenosis. It was a 9 and a half hour surgery. I have COPD, I have breathing problems.
I have breakthrough pain from RSV that's why I'm taking the medication. I don't have cancer. I had to have Actiq lollipop for dental pain. I had my teeth cut out and that's why I had the Actiq.
I have nerve damage from an accident that is way I take the medication.
I use my generic Actiq for breakthrough pain for prior surgeries. I am a chronic pain sufferer after 16 operations.
I've got a cold. My ear is stopped up. I believe it has to do with the change of seasons.
Long lasting painful conditions not caused by cancer: Yes. That' s what I use it for. I'm just an old guy with a really bad back.
Yes, but I don't have cancer.
Allergic reactions and safety instructions
are there withdrawal symptoms?
how to get off in a safe manner
I wondered over time, will it rot me teeth?

Verbatim Response
my one question was on how long it should take a Actiq to dissolve in your mouth
sorry,,,I answered incorrectly, I had a question in regard to my fentanyl patch.. the med guide said not to sunbathe...and I was wondering how the transdermal patch would be effected by the sun or heat from the sun
Was it possible to only spray half of the container?
What happens if I can't dissolve the medicine in 20min? If the first sucker doesn't not relieve the pain how soon can I take the second one?
I've been really sick and back problems. I go back and forth from the Dr. and some of the medications make me sick. Fentora makes me too sick to my stomach.
”I received this letter about Subsys. I can’t take that any more I am allergic to it.”
”I received this letter about Subsys. I can’t take that any more I am allergic to it.”

TABLE 1.1 SURVEY ADMINISTRATION STATISTICS

Question	N	%
The number of invitations issued to prescribers	1903	
The number of reminder letters mailed to prescribers	2454	
The number of respondents screened for participation	347 [1]	
The number of respondents eligible for participation	302	
The number of respondents eligible for participation who completed the survey	302	87.0
By Telephone	127	36.6
By Internet	175	50.4

[1] This is the denominator for the percentages in this table (N=347).

TABLE 1.2 TIME TO COMPLETE SURVEY (COMPLETERS ONLY)

Time to Complete Survey			
Summary Statistic	**Telephone**	**Internet**	**Total**
N	127	175	302
Mean (SD)	20.1 (5.20)	14.7 (8.37)	17.0 (7.68)
Minimum	13	6	6
Median	18.6	12.2	16.5
Maximum	44	71	71
Category	**Telephone**	**Internet**	**Total**
0 to <5 Minutes	0	0	0
5 to <10 Minutes	0	47	47
10 to <15 Minutes	5	70	75
15 to <20 Minutes	75	30	105
20 to <25 Minutes	32	15	47
25 - <30 Minutes	9	6	15
30 Minutes or More	6	7	13

TABLE 1.3 SURVEY PARTICIPANT SCREENING RESULTS

Question	All Respondents N=347		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 1: Do you agree to take part in this survey?				
Yes	346	99.7	302	100.0
No [1]	1	0.3		
Question 2: Within the last 4 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	330	95.1	301	99.7
No	14	4.0	1	0.3
I don't know	2	0.6	0	0.0
Question not asked [2]	1	0.3	0	0.0
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months? As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.				
Yes	1	0.3	1	0.3
No [1]	15	4.3		
I don't know [1]	0	0.0		
Question not asked [2]	331	95.4		
Question 5: Have you ever taken part in a survey about a TIRF medicine before?				
Yes [1]	16	4.6		
No	304	87.6	302	100.0
I don't know [1]	11	3.2		
Question not asked [2]	16	4.6		

Question	All Respondents N=347		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 6: Which of the following groups best describes your age?				
Under 18 [1]	0	0.0		
18 – 29	5	1.4	5	1.7
30 – 39	28	8.1	27	8.9
40 – 49	70	20.2	70	23.2
50 – 59	126	36.3	126	41.7
60 – 69	60	17.3	59	19.5
70 or older	15	4.3	15	5.0
Prefer not to answer [1]	0	0.0		
Question not asked [2]	43	12.4		
Question 7: Which of the following groups best describes the patient's age? (Caregivers, only)				
Under 16	0	0.0		
16 – 29	0	0.0	0	0.0
30 – 39	0	0.0	0	0.0
40 – 49	0	0.0	0	0.0
50 – 59	0	0.0	0	0.0
60 – 69	1	0.3	1	0.3
70 or older	0	0.0	0	0.0
Prefer not to answer	0	0.0		
Question not asked [2]	346	99.7		

Question	All Respondents N=347		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]				
Anesta LLC [1]	0	0.0		
Archimedes Pharma US Inc.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) [1]	0	0.0		
Endo Pharmaceuticals Inc. [1]	0	0.0		
Galena BioPharma [1]	0	0.0		
Insys Therapeutics [1]	0	0.0		
Mallinckrodt[1]	0	0.0		
McKesson Specialty Care Solutions [1]	0	0.0		
Meda Pharmaceuticals [1]	0	0.0		
Mylan, Inc.[1]	0	0.0		
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc. [1]	0	0.0		
RelayHealth [1]	0	0.0		
Teva Pharmaceuticals, Ltd. [1]	1	0.3		
United BioSource Corporation [1]	0	0.0		
FDA (Food and Drug Administration) [1]	0	0.0		
No [4]	302	87.0	302	100.0
I don't know [1]	1	0.3		

[1] Ineligible to participate in the survey.

[2] Question not asked due to a previous question elimination.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Ineligible if selected in addition to another response.

TABLE 2 DESCRIPTION OF SURVEY COMPLETERS

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months? Please select all that apply.						
Abstral	2	0.7	0	0.0	2	0.7
Actiq, including generic versions of Actiq	117	38.9	0	0.0	117	38.7
Fentora	107	35.5	0	0.0	107	35.4
Lazanda	2	0.7	0	0.0	2	0.7
Onsolis	0	0.0	0	0.0	0	0.0
Subsys	87	28.9	1	100.0	88	29.1
Other	13	4.3	0	0.0	13	4.3
I don't know	2	0.7	0	0.0	2	0.7
Question 6: Which of the following groups best describes your age?						
18 – 29	5	1.7	0	0.0	5	1.7
30 – 39	27	9.0	0	0.0	27	8.9
40 – 49	70	23.3	0	0.0	70	23.2
50 – 59	126	41.9	0	0.0	126	41.7
60 – 69	58	19.3	1	100.0	59	19.5
70 or older	15	5.0	0	0.0	15	5.0
Question 36: What is your gender?						
Male	116	38.5	1	100.0	117	38.7
Female	184	61.1	0	0.0	184	60.9
Prefer not to answer	1	0.3	0	0.0	1	0.3

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 37: What is the highest level of education you have completed?						
Less than high school	2	0.7	0	0.0	2	0.7
Some high school	6	2.0	0	0.0	6	2.0
High school graduate/GED	50	16.6	0	0.0	50	16.6
Some college/Associate's degree	140	46.5	1	100.0	141	46.7
Bachelor's degree	53	17.6	0	0.0	53	17.5
Master's degree	29	9.6	0	0.0	29	9.6
Professional or Doctoral degree	20	6.6	0	0.0	20	6.6
Prefer not to answer	1	0.3	0	0.0	1	0.3
Question 38: What is the main language you speak at home? (Please select only one.)						
English	299	99.3	1	100.0	300	99.3
French	0	0.0	0	0.0	0	0.0
Spanish	0	0.0	0	0.0	0	0.0
Portuguese	0	0.0	0	0.0	0	0.0
Italian	0	0.0	0	0.0	0	0.0
German	0	0.0	0	0.0	0	0.0
Chinese	0	0.0	0	0.0	0	0.0
Japanese	0	0.0	0	0.0	0	0.0
Korean	0	0.0	0	0.0	0	0.0
Other	1	0.3	0	0.0	1	0.3
Prefer not to answer	1	0.3	0	0.0	1	0.3
Question 39: Are you Hispanic or Latino?						
Yes	5	1.7	0	0.0	5	1.7
No	290	96.3	1	100.0	291	96.4
Prefer not to answer	6	2.0	0	0.0	6	2.0

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 40: For informational purposes only, which of the following U.S. census categories best describes your race? (Please select only one.)						
American Indian or Alaska Native	5	1.7	0	0.0	5	1.7
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	4	1.3	0	0.0	4	1.3
Black or African American	13	4.3	0	0.0	13	4.3
Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
White	266	88.4	1	100.0	267	88.4
Other	4	1.3	0	0.0	4	1.3
Prefer not to answer	9	3.0	0	0.0	9	3.0
Geographic Distribution (based on Question 41 – State or US Territory) [2]						
Northeast	113	37.5	0	0.0	113	37.4
Midwest	24	8.0	0	0.0	24	7.9
South	132	43.9	1	100.0	133	44.0
West	31	10.3	0	0.0	31	10.3
Other	0	0.0	0	0.0	0	0.0
Prefer not to answer	1	0.3	0	0.0	1	0.3

[1] Number of eligible respondents completing the survey (See Table 1).

[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

TABLE 3 RESPONSES TO ALL QUESTIONS ABOUT THE SAFE USE OF TIRF MEDICINES

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 9: Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.						
Yes	258	85.7	1	100.0	259	85.8
No	36	12.0	0	0.0	36	11.9
I don't know	7	2.3	0	0.0	7	2.3
Question 10: For which of the following conditions should I use a TIRF medicine?						
10a: Headache or migraine pain						
No [2]	233	77.4	1	100.0	234	77.5
Yes	25	8.3	0	0.0	25	8.3
I don't know	43	14.3	0	0.0	43	14.2
10b: Breakthrough pain from cancer						
Yes [2]	193	64.1	1	100.0	194	64.2
No	90	29.9	0	0.0	90	29.8
I don't know	18	6.0	0	0.0	18	6.0
10c: Dental pain						
No [2]	263	87.4	1	100.0	264	87.4
Yes	9	3.0	0	0.0	9	3.0
I don't know	29	9.6	0	0.0	29	9.6
10d: Pain after surgery						
No [2]	206	68.4	1	100.0	207	68.5
Yes	52	17.3	0	0.0	52	17.2
I don't know	43	14.3	0	0.0	43	14.2

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
10e: Long-lasting painful conditions not caused by cancer						
No [2]	65	21.6	1	100.0	66	21.9
Yes	210	69.8	0	0.0	210	69.5
I don't know	26	8.6	0	0.0	26	8.6
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True [2]	276	91.7	1	100.0	277	91.7
False	5	1.7	0	0.0	5	1.7
I don't know	20	6.6	0	0.0	20	6.6
Question 12: Please answer True, False, or I don't know for the following statements:						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.						
True [2]	266	88.4	1	100.0	267	88.4
False	12	4.0	0	0.0	12	4.0
I don't know	23	7.6	0	0.0	23	7.6
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True [2]	102	33.9	1	100.0	103	34.1
False	87	28.9	0	0.0	87	28.8
I don't know	112	37.2	0	0.0	112	37.1
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.						
False [2]	284	94.4	1	100.0	285	94.4
True	8	2.7	0	0.0	8	2.6
I don't know	9	3.0	0	0.0	9	3.0

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
False [2]	295	98.0	1	100.0	296	98.0
True	5	1.7	0	0.0	5	1.7
I don't know	1	0.3	0	0.0	1	0.3
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True [2]	301	100.0	1	100.0	302	100.0
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
13b: It is OK for patients to take TIRF medicines for headache pain.						
False [2]	205	68.1	1	100.0	206	68.2
True	21	7.0	0	0.0	21	7.0
I don't know	75	24.9	0	0.0	75	24.8
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True [2]	300	99.7	1	100.0	301	99.7
False	0	0.0	0	0.0	0	0.0
I don't know	1	0.3	0	0.0	1	0.3
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True [2]	271	90.0	1	100.0	272	90.1
False	0	0.0	0	0.0	0	0.0
I don't know	30	10.0	0	0.0	30	9.9

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away. [2]	263	87.4	1	100.0	264	87.4
Wait an hour and see if the person is OK.	17	5.6	0	0.0	17	5.6
Do nothing.	2	0.7	0	0.0	2	0.7
I don't know	19	6.3	0	0.0	19	6.3
Question 15: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for ?						
Yes	280	93.0	1	100.0	281	93.0
No	19	6.3	0	0.0	19	6.3
I don't know	2	0.7	0	0.0	2	0.7
Question 16: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?						
Yes	240	79.7	1	100.0	241	79.8
No	52	17.3	0	0.0	52	17.2
I don't know	9	3.0	0	0.0	9	3.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True [2]	296	98.3	1	100.0	297	98.3
False	2	0.7	0	0.0	2	0.7
I don't know	3	1.0	0	0.0	3	1.0
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
False [2]	251	83.4	1	100.0	252	83.4
True	15	5.0	0	0.0	15	5.0
I don't know	35	11.6	0	0.0	35	11.6

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True [2]	284	94.4	1	100.0	285	94.4
False	0	0.0	0	0.0	0	0.0
I don't know	17	5.6	0	0.0	17	5.6
17d: TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).						
True [2]	147	48.8	0	0.0	147	48.7
False	33	11.0	0	0.0	33	10.9
I don't know	121	40.2	1	100.0	122	40.4
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True [2]	274	91.0	1	100.0	275	91.1
False	2	0.7	0	0.0	2	0.7
I don't know	25	8.3	0	0.0	25	8.3

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct response

TABLE 4 RESPONSES TO QUESTIONS ABOUT TIRF MEDICATION GUIDES

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 18: Have ever received a Medication Guide for the TIRF medicine that was prescribed for you ?						
Yes	282	93.7	1	100.0	283	93.7
No	7	2.3	0	0.0	7	2.3
I don't know	12	4.0	0	0.0	12	4.0
Question 19: Did receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office? [2]						
Yes	149	52.8	1	100.0	150	53.0
No	115	40.8	0	0.0	115	40.6
I don't know	18	6.4	0	0.0	18	6.4
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	
Question 20: When was the Medication Guide given to you? Please select all that apply. [2]						
At the first appointment with the doctor who prescribed the TIRF medicine	116	77.9	1	100.0	117	78.0
At the last appointment with the doctor who prescribed the TIRF medicine	24	16.1	0	0.0	24	16.0
I don't remember	22	14.8	0	0.0	22	14.7
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 19)	152		0		152	

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 21: Did you receive the Medication Guide for the TIRF medicine from the pharmacy?[2]						
Yes	253	89.7	1	100.0	254	89.8
No	24	8.5	0	0.0	24	8.5
I don't know	5	1.8	0	0.0	5	1.8
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	
Question 22: How frequently do receive a Medication Guide for the TIRF medicine at the pharmacy? [2]						
Only with the first filled prescription	12	4.7	0	0.0	12	4.7
Each time a prescription is filled	227	89.7	1	100.0	228	89.8
Other (please specify)[3]	6	2.4	0	0.0	6	2.4
I don't know	8	3.2	0	0.0	8	3.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 21)	48		0		48	
Question 23: Did you read the Medication Guide? [2]						
Yes	267	94.7	1	100.0	268	94.7
No	13	4.6	0	0.0	13	4.6
I don't know	2	0.7	0	0.0	2	0.7
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 24: How much did you read? [2]						
All of it	169	62.8	1	100.0	170	63.0
Most of it	78	29.0	0	0.0	78	28.9
Some of it	19	7.1	0	0.0	19	7.0
I don't know	3	1.1	0	0.0	3	1.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 23)	32		0		32	
Question 25: How much of the Medication Guide did you understand? [2]						
All of it	126	46.8	0	0.0	126	46.7
Most of it	124	46.1	1	100.0	125	46.3
Some of it	18	6.7	0	0.0	18	6.7
None of it	1	0.4	0	0.0	1	0.4
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 23)	32		0		32	
Question 26: Did someone offer to explain the Medication Guide to you? [2]						
Yes	173	61.3	1	100.0	174	61.5
No	96	34.0	0	0.0	96	33.9
I don't know	13	4.6	0	0.0	13	4.6
N/A (answered ***No*** or ***I don't know*** to Question 18)	19		0		19	

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 27: Who offered to explain the Medication Guide to you? (Select all that apply.) [2]						
The doctor or another healthcare professional in the doctor's office	113	65.3	1	100.0	114	65.5
The pharmacist where the TIRF medicine prescription was filled	146	84.4	1	100.0	147	84.5
Someone else (specify the type of person but not his/her name)[4]	10	5.8	0	0.0	10	5.7
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26)	128		0		128	
Question 28: Did you accept the offer to have the Medication Guide explained to you? [2]						
Yes	110	63.6	1	100.0	111	63.8
No	61	35.3	0	0.0	61	35.1
I don't know	2	1.2	0	0.0	2	1.1
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***No*** or ***I don't know*** to Question 26)	128		0		128	

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 29: How much of the explanation did you understand? [2]						
All of it	81	73.6	0	0.0	81	73.0
Most of it	27	24.5	1	100.0	28	25.2
Some of it	2	1.8	0	0.0	2	1.8
None of it	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
N/A (answered ***No*** or ***I don't know*** to Question 18 or ***No*** or ***I don't know*** to Question 26 or ***No*** or ***I don't know*** to Question 28)	191		0		191	
Question 30: Did you or do you have any questions about the information in the Medication Guide? [2]						
Yes[5]	15	5.3	0	0.0	15	5.3
No	266	94.3	1	100.0	267	94.3
I don't know	1	0.4	0	0.0	1	0.4
N/A (answered ***No*** or I ***don't know*** to Question 18)	19		0		19	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

[3] Verbatim texts for other time receiving Medication Guide from the pharmacy are presented in Listing 1.

[4] Verbatim texts for other persons offering to explain the Medication Guide are presented in Listing 2.

[5] Questions about the information in the Medication Guide (Question 30) are presented in Listing 3.

TABLE 5 RESPONSES TO QUESTIONS ABOUT THE PATIENT-PRESCRIBER AGREEMENT FORM

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	%	N	%	N	%
Question 32: Did the doctor or someone in your doctor's office explain the Patient-Prescriber Agreement Form to you?						
Yes	222	73.8	1	100.0	223	73.8
No	43	14.3	0	0.0	43	14.2
I don't know	36	12.0	0	0.0	36	11.9
Question 33: How much of the explanation did you understand? [2]						
All of it	174	78.4	1	100.0	175	78.5
Most of it	42	18.9	0	0.0	42	18.8
Some of it	4	1.8	0	0.0	4	1.8
None of it	1	0.5	0	0.0	1	0.4
I don't know	1	0.5	0	0.0	1	0.4
N/A (answered ***No*** or ***I don't know*** to Question 32)	79		0		79	
Question 34: Did sign a Patient-Prescriber Agreement Form?						
Yes	221	73.4	1	100.0	222	73.5
No	15	5.0	0	0.0	15	5.0
I don't know	65	21.6	0	0.0	65	21.5
Question 35: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form? [2]						
Yes	150	67.9	1	100.0	151	68.0
No	38	17.2	0	0.0	38	17.1
I don't know	33	14.9	0	0.0	33	14.9
N/A (answered ***No*** or ***I don't know*** to Question 34)	80		0		80	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

TABLE 6.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True [2]	271	90.0 (86.1, 93.2)	1	100.0 (2.5, 100.0)	272	90.1 (86.1, 93.2)
False	0	0.0	0	0.0	0	0.0
I don't know	30	10.0	0	0.0	30	9.9

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct Response

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True [1]	234	94.4 (90.7, 96.9)	38	70.4 (56.4, 82.0)
False	0	0.0	0	0.0
I don't know	14	5.6	16	29.6

[1] Correct response

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
True [1]	236	94.0 (90.3, 96.6)	15	83.3 (58.6, 96.4)	1	100.0 (2.5, 100.0)	20	62.5 (43.7, 78.9)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	15	6.0	3	16.7	0	0.0	12	37.5

[1] Correct response

TABLE 6.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True [1]	41	87.2 (74.3, 95.2)	91	91.0 (83.6, 95.8)	26	92.9 (76.5, 99.1)
False	0	0.0	0	0.0	0	0.0
I don't know	6	12.8	9	9.0	2	7.1

[1] Correct response

TABLE 6.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.						
True [1]	0	0.0	70	87.5 (78.2, 93.8)	44	93.6 (82.5, 98.7)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	10	12.5	3	6.4

[1] Correct response

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True [1]	158	90.3 (84.9, 94.2)	114	89.8 (83.1, 94.4)
False	0	0.0	0	0.0
I don't know	17	9.7	13	10.2

[1] Correct response

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
True [1]	47	79.7 (67.2, 89.0)	130	92.2 (86.5, 96.0)	76	92.7 (84.8, 97.3)	19	95.0 (75.1, 99.9)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	12	20.3	11	7.8	6	7.3	1	5.0

[1] Correct response

TABLE 6.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES CAN CAUSE LIFE-THREATENING BREATHING PROBLEMS THAT CAN LEAD TO DEATH.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.								
True [1]	31	96.9 (83.8, 99.9)	62	88.6 (78.7, 94.9)	114	90.5 (84.0, 95.0)	65	87.8 (78.2, 94.3)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	3.1	8	11.4	12	9.5	9	12.2

[1] Correct response

TABLE 7.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True [2]	276	91.7 (88.0, 94.6)	1	100.0 (2.5, 100.0)	277	91.7 (88.0, 94.6)
False	5	1.7	0	0.0	5	1.7
I don't know	20	6.6	0	0.0	20	6.6
Question 12: Please answer True, False, or I don't know for the following statements.						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.						
True [2]	266	88.4 (84.2, 91.8)	1	100.0 (2.5, 100.0)	267	88.4 (84.3, 91.8)
False	12	4.0	0	0.0	12	4.0
I don't know	23	7.6	0	0.0	23	7.6
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
False [2]	205	68.1 (62.5, 73.3)	1	100.0 (2.5, 100.0)	206	68.2 (62.6, 73.4)
True	21	7.0	0	0.0	21	7.0
I don't know	75	24.9	0	0.0	75	24.8

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct response

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True [1]	230	92.7 (88.8, 95.6)	47	87.0 (75.1, 94.6)
False	5	2.0	0	0.0
I don't know	13	5.2	7	13.0
Question 12: Please answer True, False, or I don't know for the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True [1]	221	89.1 (84.6, 92.7)	46	85.2 (72.9, 93.4)
False	12	4.8	0	0.0
I don't know	15	6.0	8	14.8

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
False [1]	176	71.0 (64.9, 76.5)	30	55.6 (41.4, 69.1)
True	20	8.1	1	1.9
I don't know	52	21.0	23	42.6

[1] Correct response

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:								
TIRF medicines should only be taken by patients who are opioid tolerant.								
True [1]	233	92.8 (88.9, 95.7)	15	83.3 (58.6, 96.4)	1	100.0 (2.5, 100.0)	28	87.5 (71.0, 96.5)
False	5	2.0	0	0.0	0	0.0	0	0.0
I don't know	13	5.2	3	16.7	0	0.0	4	12.5

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True [1]	223	88.8 (84.3, 92.5)	15	83.3 (58.6, 96.4)	1	100.0 (2.5, 100.0)	28	87.5 (71.0, 96.5)
False	12	4.8	0	0.0	0	0.0	0	0.0
I don't know	16	6.4	3	16.7	0	0.0	4	12.5
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13b: It is OK for patients to take TIRF medicines for headache pain.								
False [1]	178	70.9 (64.9, 76.5)	8	44.4 (21.5, 69.2)	0	0.0	20	62.5 (43.7, 78.9)
True	20	8.0	1	5.6	0	0.0	0	0.0
I don't know	53	21.1	9	50.0	1	100.0	12	37.5

[1] Correct response

TABLE 7.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True [1]	46	97.9 (88.7, 99.9)	91	91.0 (83.6, 95.8)	25	89.3 (71.8, 97.7)
False	0	0.0	3	3.0	1	3.6
I don't know	1	2.1	6	6.0	2	7.1
Question 12: Please answer True, False, or I don't know for the following statements.						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.						
True [1]	45	95.7 (85.5, 99.5)	89	89.0 (81.2, 94.4)	24	85.7 (67.3, 96.0)
False	1	2.1	4	4.0	2	7.1
I don't know	1	2.1	7	7.0	2	7.1

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
False [1]	32	68.1 (52.9, 80.9)	68	68.0 (57.9, 77.0)	20	71.4 (51.3, 86.8)
True	3	6.4	6	6.0	0	0.0
I don't know	12	25.5	26	26.0	8	28.6

[1] Correct response

TABLE 7.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:						
TIRF medicines should only be taken by patients who are opioid tolerant.						
True [1]	0	0.0	75	93.8 (86.0, 97.9)	40	85.1 (71.7, 93.8)
False	0	0.0	1	1.3	0	0.0
I don't know	0	0.0	4	5.0	7	14.9
Question 12: Please answer True, False, or I don't know for each of the following statements.						
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.						
True [1]	0	0.0	72	90.0 (81.2, 95.6)	37	78.7 (64.3, 89.3)
False	0	0.0	2	2.5	3	6.4
I don't know	0	0.0	6	7.5	7	14.9

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13b: It is OK for patients to take TIRF medicines for headache pain.						
False [1]	0	0.0	57	71.3 (60.0, 80.8)	29	61.7 (46.4, 75.5)
True	0	0.0	5	6.3	7	14.9
I don't know	0	0.0	18	22.5	11	23.4

[1] Correct response

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True [1]	162	92.6 (87.6, 96.0)	115	90.6 (84.1, 95.0)
False	4	2.3	1	0.8
I don't know	9	5.1	11	8.7
Question 12: Please answer True, False, or I don't know for the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True [1]	158	90.3 (84.9, 94.2)	109	85.8 (78.5, 91.4)
False	7	4.0	5	3.9
I don't know	10	5.7	13	10.2
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
False [1]	120	68.6 (61.1, 75.4)	86	67.7 (58.8, 75.7)
True	9	5.1	12	9.4
I don't know	46	26.3	29	22.8

[1] Correct response

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:								
TIRF medicines should only be taken by patients who are opioid tolerant.								
True [1]	51	86.4 (75.0, 94.0)	130	92.2 (86.5, 96.0)	77	93.9 (86.3, 98.0)	19	95.0 (75.1, 99.9)
False	0	0.0	2	1.4	3	3.7	0	0.0
I don't know	8	13.6	9	6.4	2	2.4	1	5.0

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True [1]	49	83.1 (71.0, 91.6)	125	88.7 (82.2, 93.4)	76	92.7 (84.8, 97.3)	17	85.0 (62.1, 96.8)
False	3	5.1	5	3.5	2	2.4	2	10.0
I don't know	7	11.9	11	7.8	4	4.9	1	5.0
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13b: It is OK for patients to take TIRF medicines for headache pain.								
False [1]	37	62.7 (49.1, 75.0)	91	64.5 (56.0, 72.4)	62	75.6 (64.9, 84.4)	16	80.0 (56.3, 94.3)
True	5	8.5	11	7.8	5	6.1	0	0.0
I don't know	17	28.8	39	27.7	15	18.3	4	20.0

[1] Correct response

TABLE 7.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 11: Please answer True, False, or I don't know for the following statement:								
TIRF medicines should only be taken by patients who are opioid tolerant.								
True [1]	31	96.9 (83.8, 99.9)	63	90.0 (80.5, 95.9)	118	93.7 (87.9, 97.2)	65	87.8 (78.2, 94.3)
False	1	3.1	1	1.4	2	1.6	1	1.4
I don't know	0	0.0	6	8.6	6	4.8	8	10.8

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True [1]	30	93.8 (79.2, 99.2)	63	90.0 (80.5, 95.9)	112	88.9 (82.1, 93.8)	62	83.8 (73.4, 91.3)
False	2	6.3	4	5.7	4	3.2	2	2.7
I don't know	0	0.0	3	4.3	10	7.9	10	13.5
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13b: It is OK for patients to take TIRF medicines for headache pain.								
False [1]	19	59.4 (40.6, 76.3)	48	68.6 (56.4, 79.1)	83	65.9 (56.9, 74.1)	56	75.7 (64.3, 84.9)
True	2	6.3	2	2.9	11	8.7	6	8.1
I don't know	11	34.4	20	28.6	32	25.4	12	16.2

[1] Correct response

TABLE 7.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

Demonstrated Understanding	Patients N=301		Caregivers N=1		Patients & Caregivers [1] N=302	
	N	%	N	%	N	%
0 correct responses	7	2.3	0	0.0	7	2.3
1 correct response	20	6.6	0	0.0	20	6.6
2 correct responses	95	31.6	0	0.0	95	31.5
3 correct responses	179	59.5	1	100.0	180	59.6
Average number of correct responses	2.5	(2.3, 3.0) [2]	3.0	(0.2, 3.0) [2]	2.5	(2.3, 3.0) [2]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Demonstrated Understanding	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	%	N	%
0 correct responses	6	2.4	1	1.9
1 correct response	14	5.6	6	11.1
2 correct responses	71	28.6	24	44.4
3 correct responses	157	63.3	23	42.6
Average number of correct responses	2.5	(2.4, 3.0) [1]	2.3	(1.9, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	%	N	%	N	%	N	%
0 correct responses	5	2.0	1	5.6	0	0.0	1	3.1
1 correct response	16	6.4	1	5.6	0	0.0	3	9.4
2 correct responses	72	28.7	11	61.1	1	100.0	11	34.4
3 correct responses	158	62.9	5	27.8	0	0.0	17	53.1
Average number of correct responses	2.5	(2.4, 3.0) [1]	2.1	(1.5, 3.0) [1]	2.0	(-0.3, 3.0) [1]	2.4	(1.9, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	3.6
1 correct response	1	2.1	9	9.0	2	7.1
2 correct responses	16	34.0	34	34.0	8	28.6
3 correct responses	30	63.8	57	57.0	17	60.7
Average number of correct responses	2.6	(2.2, 3.0) [1]	2.5	(2.2, 3.0) [1]	2.5	(2.0, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	3	3.8	3	6.4
1 correct response	0	0.0	2	2.5	6	12.8
2 correct responses	0	0.0	23	28.8	14	29.8
3 correct responses	0	0.0	52	65.0	24	51.1
Average number of correct responses	0	(0.0, 3.0) [1]	2.6	(2.3, 3.0) [1]	2.3	(1.9, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Demonstrated Understanding	S-5a Internet N=175		S-5b Telephone N=127	
	N	%	N	%
0 correct responses	1	0.6	6	4.7
1 correct response	12	6.9	8	6.3
2 correct responses	58	33.1	37	29.1
3 correct responses	104	59.4	76	59.8
Average number of correct responses	2.5	(2.3, 3.0) [1]	2.4	(2.2, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	%	N	%	N	%	N	%
0 correct responses	2	3.4	5	3.5	0	0.0	0	0.0
1 correct response	3	5.1	10	7.1	5	6.1	2	10.0
2 correct responses	28	47.5	42	29.8	21	25.6	4	20.0
3 correct responses	26	44.1	84	59.6	56	68.3	14	70.0
Average number of correct responses	2.3	(2.0, 3.0) [1]	2.5	(2.2, 3.0) [1]	2.6	(2.3, 3.0) [1]	2.6	(2.0, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: PATIENTS SHOULD NOT TAKE TIRF MEDICINES IF THEY ARE NOT OPIOID TOLERANT.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	3	4.3	2	1.6	2	2.7
1 correct response	1	3.1	2	2.9	8	6.3	9	12.2
2 correct responses	14	43.8	23	32.9	43	34.1	15	20.3
3 correct responses	17	53.1	42	60.0	73	57.9	48	64.9
Average number of correct responses	2.5	(2.0, 3.0) [1]	2.5	(2.2, 3.0) [1]	2.5	(2.3, 3.0) [1]	2.5	(2.2, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True [2]	102	33.9 (28.6, 39.5)	1	100.0 (2.5, 100.0)	103	34.1 (28.8, 39.8)
False	87	28.9	0	0.0	87	28.8
I don't know	112	37.2	0	0.0	112	37.1
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True [2]	300	99.7 (98.2, 100.0)	1	100.0 (2.5, 100.0)	301	99.7 (98.2, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	1	0.3	0	0.0	1	0.3
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
False [2]	251	83.4 (78.7, 87.4)	1	100.0 (2.5, 100.0)	252	83.4 (78.8, 87.5)
True	15	5.0	0	0.0	15	5.0
I don't know	35	11.6	0	0.0	35	11.6

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct response

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.				
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.				
True [1]	95	38.3 (32.2, 44.7)	8	14.8 (6.6, 27.1)
False	74	29.8	13	24.1
I don't know	79	31.9	33	61.1
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True [1]	247	99.6 (97.8, 100.0)	54	100.0 (93.4, 100.0)
False	0	0.0	0	0.0
I don't know	1	0.4	0	0.0

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
False [1]	214	86.3 (81.4, 90.3)	38	70.4 (56.4, 82.0)
True	14	5.6	1	1.9
I don't know	20	8.1	15	27.8

[1] Correct response

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
True [1]	93	37.1 (31.1, 43.4)	5	27.8 (9.7, 53.5)	0	0.0	5	15.6 (5.3, 32.8)
False	77	30.7	2	11.1	0	0.0	8	25.0
I don't know	81	32.3	11	61.1	1	100.0	19	59.4

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13c: TIRF medicines should be taken exactly as prescribed by the doctor.								
True [1]	250	99.6 (97.8,100.0)	18	100.0 (81.5,100.0)	1	100.0 (2.5, 100.0)	32	100.0 (89.1,100.0)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	0.4	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
False [1]	216	86.1 (81.1, 90.1)	14	77.8 (52.4, 93.6)	0	0.0	22	68.8 (50.0, 83.9)
True	12	4.8	2	11.1	0	0.0	1	3.1
I don't know	23	9.2	2	11.1	1	100.0	9	28.1

[1] Correct response

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True [1]	20	42.6 (28.3, 57.8)	36	36.0 (26.6, 46.2)	7	25.0 (10.7, 44.9)
False	9	19.1	29	29.0	10	35.7
I don't know	18	38.3	35	35.0	11	39.3
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True [1]	47	100.0 (92.5, 100.0)	100	100.0 (96.4, 100.0)	28	100.0 (87.7, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
False [1]	42	89.4 (76.9, 96.5)	87	87.0 (78.8, 92.9)	22	78.6 (59.0, 91.7)
True	1	2.1	1	1.0	2	7.1
I don't know	4	8.5	12	12.0	4	14.3

[1] Correct response

TABLE 8.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.						
True [1]	0	0.0	28	35.0 (24.7, 46.5)	12	25.5 (13.9, 40.3)
False	0	0.0	21	26.3	18	38.3
I don't know	0	0.0	31	38.8	17	36.2
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13c: TIRF medicines should be taken exactly as prescribed by the doctor.						
True [1]	0	0.0	79	98.8 (93.2, 100.0)	47	100.0 (92.5, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	1	1.3	0	0.0

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.						
False [1]	0	0.0	65	81.3 (71.0, 89.1)	36	76.6 (62.0, 87.7)
True	0	0.0	6	7.5	5	10.6
I don't know	0	0.0	9	11.3	6	12.8

[1] Correct response

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.				
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.				
True [1]	63	36.0 (28.9, 43.6)	40	31.5 (23.5, 40.3)
False	48	27.4	39	30.7
I don't know	64	36.6	48	37.8
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True [1]	175	100.0 (97.9, 100.0)	126	99.2 (95.7, 100.0)
False	0	0.0	0	0.0
I don't know	0	0.0	1	0.8
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
False [1]	151	86.3 (80.3, 91.0)	101	79.5 (71.5, 86.2)
True	4	2.3	11	8.7
I don't know	20	11.4	15	11.8

[1] Correct response

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
True [1]	20	33.9 (22.1, 47.4)	55	39.0 (30.9, 47.6)	21	25.6 (16.6, 36.4)	7	35.0 (15.4, 59.2)
False	15	25.4	40	28.4	24	29.3	8	40.0
I don't know	24	40.7	46	32.6	37	45.1	5	25.0

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13c: TIRF medicines should be taken exactly as prescribed by the doctor.								
True [1]	59	100.0 (93.9, 100.0)	140	99.3 (96.1, 100.0)	82	100.0 (95.6, 100.0)	20	100.0 (83.2, 100.0)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	1	0.7	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
False [1]	46	78.0 (65.3, 87.7)	121	85.8 (78.9, 91.1)	68	82.9 (73.0, 90.3)	17	85.0 (62.1, 96.8)
True	3	5.1	5	3.5	7	8.5	0	0.0
I don't know	10	16.9	15	10.6	7	8.5	3	15.0

[1] Correct response

TABLE 8.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12b: If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.								
True [1]	12	37.5 (21.1, 56.3)	23	32.9 (22.1, 45.1)	43	34.1 (25.9, 43.1)	25	33.8 (23.2, 45.7)
False	8	25.0	22	31.4	39	31.0	18	24.3
I don't know	12	37.5	25	35.7	44	34.9	31	41.9

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13c: TIRF medicines should be taken exactly as prescribed by the doctor.								
True [1]	32	100.0 (89.1, 100.0)	70	100.0 (94.9, 100.0)	125	99.2 (95.7, 100.0)	74	100.0 (95.1, 100.0)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	1	0.8	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.								
False [1]	29	90.6 (75.0, 98.0)	61	87.1 (77.0, 93.9)	103	81.7 (73.9, 88.1)	59	79.7 (68.8, 88.2)
True	0	0.0	2	2.9	8	6.3	5	6.8
I don't know	3	9.4	7	10.0	15	11.9	10	13.5

[1] Correct response

TABLE 8.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

Demonstrated Understanding	Patients N=301		Caregivers N=1		Patients & Caregivers [1] N=302	
	N	%	N	%	N	%
0 correct responses	1	0.3	0	0.0	1	0.3
1 correct response	40	13.3	0	0.0	40	13.2
2 correct responses	167	55.5	0	0.0	167	55.3
3 correct responses	93	30.9	1	100.0	94	31.1
Average number of correct responses	2.2	(2.0, 3.0)[2]	3.0	(0.2, 3.0) [2]	2.2	(2.0, 3.0) [2]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Demonstrated Understanding	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	%	N	%
0 correct responses	1	0.4	0	0.0
1 correct response	25	10.1	15	27.8
2 correct responses	135	54.4	32	59.3
3 correct responses	87	35.1	7	13.0
Average number of correct responses	2.2	(2.1, 3.0) [1]	1.9	(1.5, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	%	N	%	N	%	N	%
0 correct responses	1	0.4	0	0.0	0	0.0	0	0.0
1 correct response	28	11.2	2	11.1	1	100.0	9	28.1
2 correct responses	135	53.8	13	72.2	0	0.0	19	59.4
3 correct responses	87	34.7	3	16.7	0	0.0	4	12.5
Average number of correct responses	2.2	(2.1, 3.0) [1]	2.1	(1.5, 3.0) [1]	1.0	(-0.6, 3.0)[1]	1.8	(1.4, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	4	8.5	13	13.0	5	17.9
2 correct responses	24	51.1	51	51.0	17	60.7
3 correct responses	19	40.4	36	36.0	6	21.4
Average number of correct responses	2.3	(2.0, 3.0) [1]	2.2	(2.0, 3.0) [1]	2.0	(1.6, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	1	1.3	0	0.0
1 correct response	0	0.0	8	10.0	10	21.3
2 correct responses	0	0.0	49	61.3	26	55.3
3 correct responses	0	0.0	22	27.5	11	23.4
Average number of correct responses	0	(0.0, 3.0) [1]	2.2	(1.9, 3.0) [1]	2.0	(1.7, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Demonstrated Understanding	S-5a Internet N=175		S-5b Telephone N=127	
	N	%	N	%
0 correct responses	0	0.0	1	0.8
1 correct response	22	12.6	18	14.2
2 correct responses	92	52.6	75	59.1
3 correct responses	61	34.9	33	26.0
Average number of correct responses	2.2	(2.0, 3.0) [1]	2.1	(1.9, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	1	0.7	0	0.0	0	0.0
1 correct response	9	15.3	17	12.1	12	14.6	2	10.0
2 correct responses	34	57.6	70	49.6	51	62.2	12	60.0
3 correct responses	16	27.1	53	37.6	19	23.2	6	30.0
Average number of correct responses	2.1	(1.8, 3.0) [1]	2.2	(2.0, 3.0) [1]	2.1	(1.8, 3.0) [1]	2.2	(1.7, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES SHOULD BE TAKEN EXACTLY AS PRESCRIBED BY THE HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	0.8	0	0.0
1 correct response	3	9.4	8	11.4	17	13.5	12	16.2
2 correct responses	17	53.1	40	57.1	70	55.6	40	54.1
3 correct responses	12	37.5	22	31.4	38	30.2	22	29.7
Average number of correct responses	2.3	(1.8, 3.0) [1]	2.2	(1.9, 3.0) [1]	2.2	(1.9, 3.0) [1]	2.1	(1.9, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.						
False [2]	284	94.4 (91.1, 96.7)	1	100.0 (2.5, 100.0)	285	94.4 (91.1, 96.7)
True	8	2.7	0	0.0	8	2.6
I don't know	9	3.0	0	0.0	9	3.0

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct response

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
False [1]	233	94.0 (90.2, 96.6)	52	96.3 (87.3, 99.5)
True	7	2.8	1	1.9
I don't know	8	3.2	1	1.9

[1] Correct response

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False [1]	237	94.4 (90.8, 96.9)	17	94.4 (72.7, 99.9)	1	100.0 (2.5, 100.0)	30	93.8 (79.2, 99.2)
True	7	2.8	0	0.0	0	0.0	1	3.1
I don't know	7	2.8	1	5.6	0	0.0	1	3.1

[1] Correct response

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.						
False [1]	47	100.0 (92.5, 100.0)	96	96.0 (90.1, 98.9)	26	92.9 (76.5, 99.1)
True	0	0.0	1	1.0	1	3.6
I don't know	0	0.0	3	3.0	1	3.6

[1] Correct response

TABLE 9.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.						
False [1]	0	0.0	75	93.8 (86.0, 97.9)	41	87.2 (74.3, 95.2)
True	0	0.0	3	3.8	3	6.4
I don't know	0	0.0	2	2.5	3	6.4

[2] Correct response

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
False [1]	169	96.6 (92.7, 98.7)	116	91.3 (85.0, 95.6)
True	2	1.1	6	4.7
I don't know	4	2.3	5	3.9

[1] Correct response

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False [1]	54	91.5 (81.3, 97.2)	132	93.6 (88.2, 97.0)	79	96.3 (89.7, 99.2)	20	100.0 (83.2, 100.0)
True	3	5.1	2	1.4	3	3.7	0	0.0
I don't know	2	3.4	7	5.0	0	0.0	0	0.0

[1] Correct response

TABLE 9.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: PATIENTS SHOULD NOT SWITCH FROM A TIRF MEDICINE TO ANOTHER MEDICINE THAT CONTAINS FENTANYL WITHOUT TALKING TO A HEALTHCARE PROVIDER.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for each of the following statements.								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False [1]	32	100.0 (89.1, 100.0)	67	95.7 (88.0, 99.1)	118	93.7 (87.9, 97.2)	68	91.9 (83.2, 97.0)
True	0	0.0	0	0.0	4	3.2	4	5.4
I don't know	0	0.0	3	4.3	4	3.2	2	2.7

[1] Correct response

TABLE 10.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
False [2]	295	98.0 (95.7, 99.3)	1	100.0 (2.5, 100.0)	296	98.0 (95.7, 99.3)
True	5	1.7	0	0.0	5	1.7
I don't know	1	0.3	0	0.0	1	0.3
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True [2]	296	98.3 (96.2, 99.5)	1	100.0 (2.5, 100.0)	297	98.3 (96.2, 99.5)
False	2	0.7	0	0.0	2	0.7
I don't know	3	1.0	0	0.0	3	1.0

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct response

TABLE 10.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
False [1]	243	98.0 (95.4, 99.3)	53	98.1 (90.1, 100.0)
True	4	1.6	1	1.9
I don't know	1	0.4	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True [1]	245	98.8 (96.5, 99.7)	52	96.3 (87.3, 99.5)
False	1	0.4	1	1.9
I don't know	2	0.8	1	1.9

[1] Correct response

TABLE 10.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
False [1]	246	98.0 (95.4, 99.4)	18	100.0 (81.5, 100.0)	1	100.0 (2.5, 100.0)	31	96.9 (83.8, 99.9)
True	4	1.6	0	0.0	0	0.0	1	3.1
I don't know	1	0.4	0	0.0	0	0.0	0	0.0

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17a: Selling or giving away TIRF medicines is against the law.								
True [1]	247	98.4 (96.0, 99.6)	18	100.0 (81.5, 100.0)	1	100.0 (2.5, 100.0)	31	96.9 (83.8, 99.9)
False	1	0.4	0	0.0	0	0.0	1	3.1
I don't know	3	1.2	0	0.0	0	0.0	0	0.0

[1] Correct response

TABLE 10.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
False [1]	46	97.9 (88.7, 99.9)	100	100.0 (96.4, 100.0)	28	100.0 (87.7, 100.0)
True	1	2.1	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True [1]	47	100.0 (92.5, 100.0)	97	97.0 (91.5, 99.4)	28	100.0 (87.7, 100.0)
False	0	0.0	1	1.0	0	0.0
I don't know	0	0.0	2	2.0	0	0.0

[1] Correct response

TABLE 10.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.						
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.						
False [1]	0	0.0	77	96.3 (89.4, 99.2)	45	95.7 (85.5, 99.5)
True	0	0.0	2	2.5	2	4.3
I don't know	0	0.0	1	1.3	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17a: Selling or giving away TIRF medicines is against the law.						
True [1]	0	0.0	78	97.5 (91.3, 99.7)	47	100.0 (92.5, 100.0)
False	0	0.0	1	1.3	0	0.0
I don't know	0	0.0	1	1.3	0	0.0

[1] Correct response

TABLE 10.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
False [1]	174	99.4 (96.9, 100.0)	122	96.1 (91.1, 98.7)
True	1	0.6	4	3.1
I don't know	0	0.0	1	0.8
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True [1]	172	98.3 (95.1, 99.6)	125	98.4 (94.4, 99.8)
False	1	0.6	1	0.8
I don't know	2	1.1	1	0.8

[1] Correct response

TABLE 10.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
False [1]	58	98.3 (90.9, 100.0)	136	96.5 (91.9, 98.8)	82	100.0 (95.6, 100.0)	20	100.0 (83.2, 100.0)
True	1	1.7	4	2.8	0	0.0	0	0.0
I don't know	0	0.0	1	0.7	0	0.0	0	0.0

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17a: Selling or giving away TIRF medicines is against the law.								
True [1]	57	96.6 (88.3, 99.6)	140	99.3 (96.1, 100.0)	82	100.0 (95.6, 100.0)	18	90.0 (68.3, 98.8)
False	1	1.7	1	0.7	0	0.0	0	0.0
I don't know	1	1.7	0	0.0	0	0.0	2	10.0

[1] Correct response

TABLE 10.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 12: Please answer True, False, or I don't know for the following statements.								
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.								
False [1]	32	100.0 (89.1, 100.0)	70	100.0 (94.9, 100.0)	121	96.0 (91.0, 98.7)	73	98.6 (92.7, 100.0)
True	0	0.0	0	0.0	4	3.2	1	1.4
I don't know	0	0.0	0	0.0	1	0.8	0	0.0

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17a: Selling or giving away TIRF medicines is against the law.								
True [1]	32	100.0 (89.1, 100.0)	70	100.0 (94.9, 100.0)	123	97.6 (93.2, 99.5)	72	97.3 (90.6, 99.7)
False	0	0.0	0	0.0	1	0.8	1	1.4
I don't know	0	0.0	0	0.0	2	1.6	1	1.4

[1] Correct response

TABLE 10.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

Demonstrated Understanding	Patients N=301		Caregivers N=1		Patients & Caregivers [1] N=302	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	11	3.7	0	0.0	11	3.6
2 correct responses	290	96.3	1	100.0	291	96.4
Average number of correct responses	2.0	(1.8, 2.0) [2]	2.0	(-0.3, 2.0) [2]	2.0	(1.8, 2.0) [2]

[1] Number of eligible respondents completing the survey (See Table 1).

[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Demonstrated Understanding	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	8	3.2	3	5.6
2 correct responses	240	96.8	51	94.4
Average number of correct responses	2.0	(1.8, 2.0) [1]	1.9	(1.6, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	9	3.6	0	0.0	0	0.0	2	6.3
2 correct responses	242	96.4	18	100.0	1	100.0	30	93.8
Average number of correct responses	2.0	(1.8, 2.0) [1]	2.0	(1.5, 2.0) [1]	2.0	(-0.3, 2.0) [1]	1.9	(1.5, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.1	3	3.0	0	0.0
2 correct responses	46	97.9	97	97.0	28	100.0
Average number of correct responses	2.0	(1.6, 2.0) [1]	2.0	(1.7, 2.0) [1]	2.0	(1.6, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	5	6.3	2	4.3
2 correct responses	0	0.0	75	93.8	45	95.7
Average number of correct responses	0	(0.0, 2.0) [1]	1.9	(1.7, 2.0) [1]	2.0	(1.6, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Demonstrated Understanding	S-5a Internet N=175		S-5b Telephone N=127	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	4	2.3	7	5.5
2 correct responses	171	97.7	120	94.5
Average number of correct responses	2.0	(1.8, 2.0) [1]	1.9	(1.7, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	3	5.1	6	4.3	0	0.0	2	10.0
2 correct responses	56	94.9	135	95.7	82	100.0	18	90.0
Average number of correct responses	1.9	(1.7, 2.0) [1]	2.0	(1.8, 2.0) [1]	2.0	(1.7, 2.0) [1]	1.9	(1.4, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 10.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #5

KEY RISK MESSAGE 5: PATIENTS SHOULD NOT GIVE TIRF MEDICINES TO ANYONE ELSE EVEN IF THEY HAVE THE SAME SYMPTOMS.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	8	6.3	3	4.1
2 correct responses	32	100.0	70	100.0	118	93.7	71	95.9
Average number of correct responses	2.0	(1.6, 2.0) [1]	2.0	(1.7, 2.0) [1]	1.9	(1.7, 2.0) [1]	2.0	(1.7, 2.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True [2]	301	100.0 (98.8, 100.0)	1	100.0 (2.5, 100.0)	302	100.0 (98.8, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True [2]	284	94.4 (91.1, 96.7)	1	100.0 (2.5, 100.0)	285	94.4 (91.1, 96.7)
False	0	0.0	0	0.0	0	0.0
I don't know	17	5.6	0	0.0	17	5.6
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True [2]	274	91.0 (87.2, 94.0)	1	100.0 (2.5, 100.0)	275	91.1 (87.3, 94.0)
False	2	0.7	0	0.0	2	0.7
I don't know	25	8.3	0	0.0	25	8.3

Question	Patients N=301		Caregivers N=1		Patients & Caregivers[1] N=302	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away. [2]	263	87.4 (83.1, 90.9)	1	100.0 (2.5, 100.0)	264	87.4 (83.1, 90.9)
Wait an hour and see if the person is OK.	17	5.6	0	0.0	17	5.6
Do nothing.	2	0.7	0	0.0	2	0.7
I don't know	19	6.3	0	0.0	19	6.3

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Correct response

TABLE 11.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True [1]	248	100.0 (98.5, 100.0)	54	100.0 (93.4, 100.0)
False	0	0.0	0	0.0
I don't know	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True [1]	241	97.2 (94.3, 98.9)	44	81.5 (68.6, 90.7)
False	0	0.0	0	0.0
I don't know	7	2.8	10	18.5

Question	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	% (95% CI)	N	% (95% CI)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True [1]	230	92.7 (88.8, 95.6)	45	83.3 (70.7, 92.1)
False	2	0.8	0	0.0
I don't know	16	6.5	9	16.7
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Get emergency help right away. [1]	222	89.5 (85.0, 93.0)	42	77.8 (64.4, 88.0)
Wait an hour and see if the person is OK.	13	5.2	4	7.4
Do nothing.	2	0.8	0	0.0
I don't know	11	4.4	8	14.8

[1] Correct response

TABLE 11.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13a: TIRF medicines should be stored in a safe place out of the reach of children.								
True [1]	251	100.0 (98.5, 100.0)	18	100.0 (81.5, 100.0)	1	100.0 (2.5, 100.0)	32	100.0 (89.1, 100.0)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
True [1]	245	97.6 (94.9, 99.1)	15	83.3 (58.6, 96.4)	1	100.0 (2.5, 100.0)	24	75.0 (56.6, 88.5)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	6	2.4	3	16.7	0	0.0	8	25.0
17e: A TIRF medicine can cause an overdose and death in any child who takes it.								
True [1]	230	91.6 (87.5, 94.7)	17	94.4 (72.7, 99.9)	0	0.0	28	87.5 (71.0, 96.5)
False	2	0.8	0	0.0	0	0.0	0	0.0
I don't know	19	7.6	1	5.6	1	100.0	4	12.5

Question	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away. [1]	223	88.8 (84.3, 92.5)	16	88.9 (65.3, 98.6)	0	0.0	25	78.1 (60.0, 90.7)
Wait an hour and see if the person is OK.	14	5.6	0	0.0	0	0.0	3	9.4
Do nothing.	2	0.8	0	0.0	0	0.0	0	0.0
I don't know	12	4.8	2	11.1	1	100.0	4	12.5

[1] Correct response

TABLE 11.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True [1]	47	100.0 (92.5, 100.0)	100	100.0 (96.4, 100.0)	28	100.0 (87.7, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True [1]	45	95.7 (85.5, 99.5)	94	94.0 (87.4, 97.8)	26	92.9 (76.5, 99.1)
False	0	0.0	0	0.0	0	0.0
I don't know	2	4.3	6	6.0	2	7.1
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True [1]	46	97.9 (88.7, 99.9)	90	90.0 (82.4, 95.1)	27	96.4 (81.7, 99.9)
False	0	0.0	1	1.0	0	0.0

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
I don't know	1	2.1	9	9.0	1	3.6
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away. [1]	44	93.6 (82.5, 98.7)	86	86.0 (77.6, 92.1)	23	82.1 (63.1, 93.9)
Wait an hour and see if the person is OK.	1	2.1	5	5.0	0	0.0
Do nothing.	0	0.0	1	1.0	1	3.6
I don't know	2	4.3	8	8.0	4	14.3

[1] Correct response

TABLE 11.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
13a: TIRF medicines should be stored in a safe place out of the reach of children.						
True [1]	0	0.0	80	100.0 (95.5, 100.0)	47	100.0 (92.5, 100.0)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.						
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.						
True [1]	0	0.0	75	93.8 (86.0, 97.9)	45	95.7 (85.5, 99.5)
False	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	5	6.3	2	4.3

Question	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.						
True [1]	0	0.0	73	91.3 (82.8, 96.4)	39	83.0 (69.2, 92.4)
False	0	0.0	1	1.3	0	0.0
I don't know	0	0.0	6	7.5	8	17.0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)						
Get emergency help right away. [1]	0	0.0	71	88.8 (79.7, 94.7)	40	85.1 (71.7, 93.8)
Wait an hour and see if the person is OK.	0	0.0	7	8.8	4	8.5
Do nothing.	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	2	2.5	3	6.4

[1] Correct response

TABLE 11.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True [1]	175	100.0 (97.9, 100.0)	127	100.0 (97.1, 100.0)
False	0	0.0	0	0.0
I don't know	0	0.0	0	0.0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True [1]	165	94.3 (89.7, 97.2)	120	94.5 (89.0, 97.8)
False	0	0.0	0	0.0
I don't know	10	5.7	7	5.5
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True [1]	163	93.1 (88.3, 96.4)	112	88.2 (81.3, 93.2)
False	1	0.6	1	0.8
I don't know	11	6.3	14	11.0

Question	S-5a Internet N=175		S-5b Telephone N=127	
	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Get emergency help right away. [1]	153	87.4 (81.6, 92.0)	111	87.4 (80.3, 92.6)
Wait an hour and see if the person is OK.	6	3.4	11	8.7
Do nothing.	2	1.1	0	0.0
I don't know	14	8.0	5	3.9

[1] Correct response

TABLE 11.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13a: TIRF medicines should be stored in a safe place out of the reach of children.								
True [1]	59	100.0 (93.9, 100.0)	141	100.0 (97.4, 100.0)	82	100.0 (95.6, 100.0)	20	100.0 (83.2, 100.0)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
True [1]	53	89.8 (79.2, 96.2)	132	93.6 (88.2, 97.0)	81	98.8 (93.4, 100.0)	19	95.0 (75.1, 99.9)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	6	10.2	9	6.4	1	1.2	1	5.0
17e: A TIRF medicine can cause an overdose and death in any child who takes it.								
True [1]	52	88.1 (77.1, 95.1)	129	91.5 (85.6, 95.5)	76	92.7 (84.8, 97.3)	18	90.0 (68.3, 98.8)
False	1	1.7	0	0.0	0	0.0	1	5.0
I don't know	6	10.2	12	8.5	6	7.3	1	5.0

Question	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away. [1]	50	84.7 (73.0, 92.8)	128	90.8 (84.7, 95.0)	72	87.8 (78.7, 94.0)	14	70.0 (45.7, 88.1)
Wait an hour and see if the person is OK.	3	5.1	8	5.7	5	6.1	1	5.0
Do nothing.	0	0.0	1	0.7	1	1.2	0	0.0
I don't know	6	10.2	4	2.8	4	4.9	5	25.0

[1] Correct response

TABLE 11.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
13a: TIRF medicines should be stored in a safe place out of the reach of children.								
True [1]	32	100.0 (89.1, 100.0)	70	100.0 (94.9, 100.0)	126	100.0 (97.1, 100.0)	74	100.0 (95.1, 100.0)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	0	0.0

Question	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.								
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.								
True [1]	32	100.0 (89.1,100.0)	65	92.9 (84.1, 97.6)	121	96.0 (91.0, 98.7)	67	90.5 (81.5, 96.1)
False	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	5	7.1	5	4.0	7	9.5
17e: A TIRF medicine can cause an overdose and death in any child who takes it.								
True [1]	27	84.4 (67.2, 94.7)	64	91.4 (82.3, 96.8)	119	94.4 (88.9, 97.7)	65	87.8 (78.2, 94.3)
False	1	3.1	1	1.4	0	0.0	0	0.0
I don't know	4	12.5	5	7.1	7	5.6	9	12.2
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away. [1]	29	90.6 (75.0, 98.0)	63	90.0 (80.5, 95.9)	108	85.7 (78.4, 91.3)	64	86.5 (76.5, 93.3)
Wait an hour and see if the person is OK.	1	3.1	3	4.3	8	6.3	5	6.8
Do nothing.	0	0.0	0	0.0	1	0.8	1	1.4
I don't know	2	6.3	4	5.7	9	7.1	4	5.4

[1] Correct response

TABLE 11.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

Demonstrated Understanding	Patients N=301		Caregivers N=1		Patients & Caregivers [1] N=302	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	2	0.7	0	0.0	2	0.7
2 correct responses	13	4.3	0	0.0	13	4.3
3 correct responses	50	16.6	0	0.0	50	16.6
4 correct responses	236	78.4	1	100.0	237	78.5
Average number of correct responses	3.7	(3.5, 4.0) [2]	4.0	(0.7, 4.0) [2]	3.7	(3.5, 4.0) [2]

[1] Number of eligible respondents completing the survey (See Table 1).
[2] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE (QUESTION 18, 23 AND 24)

- **S-1a - Respondents who received the Medication Guide and read at least most of it**
- **S-1b - Respondents who did not receive a Medication Guide or answered "I don't know" or who received a Medication Guide and read only some of it or answered "I don't know".**

Demonstrated Understanding	S-1a Read most of Med Guide N=248		S-1b Read some or none of Med Guide N=54	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	2	3.7
2 correct responses	7	2.8	6	11.1
3 correct responses	37	14.9	13	24.1
4 correct responses	204	82.3	33	61.1
Average number of correct responses	3.8	(3.6, 4.0) [1]	3.4	(3.0, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 2: UNDERSTANDING OF MEDICATION GUIDE (QUESTION 25)

- **S-2a - Respondents who understood all of it or most of it**
- **S-2b – Respondents who understood some of it**
- **S-2c – Respondents who answered None or "I don't know"**
- **S-2d - Respondents who answered "I don't know" to receipt or reading of the Medication Guide.**

Demonstrated Understanding	S-2a Understood All or Most N=251		S-2b Understood Some N=18		S-2c None/I don't know N=1		S-2d Did not Get or Read Medication Guide N=32	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	1	0.4	0	0.0	0	0.0	1	3.1
2 correct responses	6	2.4	1	5.6	1	100.0	5	15.6
3 correct responses	40	15.9	4	22.2	0	0.0	6	18.8
4 correct responses	204	81.3	13	72.2	0	0.0	20	62.5
Average number of correct responses	3.8	(3.6, 4.0) [1]	3.7	(2.9, 4.0) [1]	2.0	(-0.3, 4.0) [1]	3.4	(2.9, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY - INTERNET:

- **S-3a - <10 min**
- **S-3b - 10 to<20 min**
- **S-3c - ≥20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=100		S-3c ≥20 min N=28	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	2	2.0	0	0.0
2 correct responses	1	2.1	5	5.0	2	7.1
3 correct responses	4	8.5	14	14.0	4	14.3
4 correct responses	42	89.4	79	79.0	22	78.6
Average number of correct responses	3.9	(3.4, 4.0) [1]	3.7	(3.4, 4.0) [1]	3.7	(3.1, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 4: TIME TO COMPLETE SURVEY - TELEPHONE:

- **S-4a - <10 min**
- **S-4b - 10 to<20 min**
- **S-4c - ≥20 min**

Demonstrated Understanding	S-4a <10 min N=0		S-4b 10 to <20 min N=80		S-4c ≥20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0
2 correct responses	0	0.0	2	2.5	3	6.4
3 correct responses	0	0.0	17	21.3	11	23.4
4 correct responses	0	0.0	61	76.3	33	70.2
Average number of correct responses	0	(0.0, 4.0) [1]	3.7	(3.4, 4.0) [1]	3.6	(3.2, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b – Telephone**

Demonstrated Understanding	S-5a - Internet N=175		S-5b - Telephone N=127	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	2	1.1	0	0.0
2 correct responses	8	4.6	5	3.9
3 correct responses	22	12.6	28	22.0
4 correct responses	143	81.7	94	74.0
Average number of correct responses	3.7	(3.5, 4.0) [1]	3.7	(3.4, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 6: HIGHEST LEVEL OF EDUCATION (QUESTION 37):

- **S-6a - Less than, Some, or High school graduate/GED or prefer not to answer**
- **S-6b - Some college or associate degree**
- **S-6c - Bachelor's degree or Master's degree**
- **S-6d - Professional or Doctoral degree**

Demonstrated Understanding	S-6a High School N=59		S-6b Some college N=141		S-6c Bachelor or Master N=82		S-6d Doctoral degree N=20	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	1	1.7	0	0.0	0	0.0	1	5.0
2 correct responses	3	5.1	7	5.0	3	3.7	0	0.0
3 correct responses	13	22.0	20	14.2	11	13.4	6	30.0
4 correct responses	42	71.2	114	80.9	68	82.9	13	65.0
Average number of correct responses	3.6	(3.2, 4.0) [1]	3.8	(3.5, 4.0) [1]	3.8	(3.4, 4.0) [1]	3.6	(2.9, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 11.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #6

KEY RISK MESSAGE 6: TIRF MEDICINES SHOULD BE STORED IN A SAFE PLACE AWAY FROM CHILDREN AND PROPERLY DISPOSED.

SUB-GROUP ANALYSIS 7: AGE GROUP OF RESPONDENT (QUESTION 6):

- **S-7a – 18 to 39**
- **S-7b – 40 to 49**
- **S-7c – 50 to 59**
- **S-7d – 60 or older**

Demonstrated Understanding	S-7a 18 to 39 N=32		S-7b 40 to 49 N=70		S-7c 50 to 59 N=126		S-7d 60 or older N=74	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	0.8	1	1.4
2 correct responses	1	3.1	2	2.9	4	3.2	6	8.1
3 correct responses	6	18.8	14	20.0	19	15.1	11	14.9
4 correct responses	25	78.1	54	77.1	102	81.0	56	75.7
Average number of correct responses	3.8	(3.2, 4.0) [1]	3.7	(3.4, 4.0) [1]	3.8	(3.5, 4.0) [1]	3.6	(3.3, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

Appendix C Patient Survey Protocol Track Change Document: Comparison of 12-month Survey to 24-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Archimedes Pharma US Inc.** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Endo Pharmaceuticals Inc.** **Galena Biopharma** **Insys Therapeutics** **Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**6~~4~~.0**
DATE:	**10 Sep~~22 May~~ 2013**
APPROVED:	**FINAL**

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LIST OF APPENDICES

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FDA_1056

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KAB	Knowledge, Attitudes and Behavior
PBM	Pharmacy Benefits Management
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SE/PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

FDA_1057

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics, which are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between TIRF medicines
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines, as described in the product-specific Medication Guide. This protocol will describe the administration of the surveys that will be conducted among patients who are treated with TIRF medicines, or their caregivers. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS.

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The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients around the following key information and risk messages communicated through the REMS:

1) TIRF medicines can cause life-threatening breathing problems that can lead to death.
2) Patients should not take TIRF medicines if they are not opioid tolerant.
3) TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4) Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5) Patients should not give TIRF medicines to anyone else even if they have the same symptoms.
6) TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey will also include questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of patients who have filled a prescription for a TIRF medicine within the past 43 months prior to survey launch and their caregivers. Respondents who have participated in a previous wave of the TIRF REMS KAB survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix B is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

4.1.1 Questions and Statements on REMS Goals

The KAB items of the questionnaire are made up of multiple-choice, closed-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and open-ended questions. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3. The survey is written to follow principles of health literacy and readability.

Questionnaire items will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes," "no," or "I don't know" as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- Questions allowing for the respondent to provide information about when, where and from whom they obtained a Medication Guide, as well as to list questions about information in the Medication Guides.

Questionnaires will be analyzed to determine patient understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, the patient questions, only, are presented in the key risk messages tables. Caregiver questions are presented in Appendix A.

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Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
1312	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d12d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
1110	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**
1211	Please answer True, False, or I don't know for each of the following statements.	
12a11a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**
1312	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b12b	It is OK for patients to take TIRF medicines for headache pain.	**FALSE**

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
1211	Please answer True, False, or I don't know for each of the following statements.	

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12b~~11b~~	If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	**TRUE**
13/17~~12/16~~	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c~~12c~~	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
17b~~16b~~	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**

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Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12~~11~~	Please answer True, False, or I don't know for each of the following statements.	
12c~~11c~~	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**

Key Risk Message 5: Patients should not give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12~~11~~	Please answer True, False, or I don't know for each of the following statements.	
12d~~11d~~	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
17~~16a~~	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a~~16a~~	Selling or giving away TIRF medicines is against the law.	**TRUE**

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Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/1712/16	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a12a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
17c16c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
17e16e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**
1313	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**Get emergency help right away.**

4.1.2 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and PPAF will be asked after the key risk message questions, and will be followed by the collection of demographic information at the completion of the survey.

4.2 Subject Recruitment

Patients will be recruited through a direct letter program. Patients will be invited through a network of national pharmacies and a~~pharmacy chain network partner or~~ pharmacy benefits management (PBM) partner, which each have broad demographic coverage and include patients in 49 states. Leveraging one or more of these partners, a list will be created of patients who have filled a prescription for a TIRF medicine within 43 months prior to survey launch (first prescriptions and refills). Patients in this list will be invited to participate in the survey through an invitation letter (Appendix B) mailed directly to the patients on the pharmacy or PBM's letterhead at the corporate level via the United States (US) Postal Service.

Additionally, outbound calls will be placed to prescribers to ask for their support in informing patients about the opportunity to participate in the survey by providing an invitation directly to patients who are prescribed a TIRF medicine. A random sample of up to 250 prescribers with at least 5 patients who have filled prescriptions in the 4 months prior to survey implementation will be contacted for this purpose. If a prescriber expresses willingness to support the survey effort, an information packet including invitation letters will be mailed to the prescriber. Prescribers will not receive any compensation for this support.

The invitation will indicate that participants will receive a $5025 gift card for completing the survey. Each invitation will also include a unique code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. The unique code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.

A random sample of patients who have filled a prescription for a TIRF medicine within the 43 months prior to survey launch will be chosen from the pharmacy partner's or PBM database. This sampling approach will be used to create several batches of survey invitations. The overall number of unique patients and the duration of the survey period will dictate the size and number of invitation batches. If the required number of completed surveys is not achieved within a reasonable time frame, a second mailing will be sent to non-respondents from the original batch mailing and initial invitations will be sent to patients in the second batch. If the required number of completed surveys is still not achieved within a reasonable time frame, reminder letters will be sent to the patients in the second batch and initial invitations will be sent to the third batch of patients. If these efforts do not result in the required number of surveys within a reasonable time frame, then a new random sample of patients may be selected. The intervals for sending reminder invitations to non-responders and for selecting a new sample will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

All respondents who complete the survey and who provide their contact information will be mailed a $5025 gift card to thank them for their participation. The mailing will include a thank you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating patients will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of patients for participation.

Respondents will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

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5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 patients treated with TIRF medicines is proposed for the survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each key risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

The following respondents are eligible to participate in the survey:

- Patients who are 18 years of age or older who have filled a prescription for at least one of the TIRF medicines within 43 months prior to survey launch
- Caregivers 18 years of age or older who care for patients who have filled a TIRF medicine prescription within the past 43 months prior to survey launch and are unable to take the survey for themselves

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5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Patients who have previously participated in the TIRF REMS KAB survey (this exclusion applies to the second and subsequent waves only)
- Patients or their immediate family members who have ever worked for Anesta LLC, Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; ProStrakan Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm patient eligibility. The entire survey is expected to take approximately 20 minutes to complete. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, respondents are immediately notified with a thank you message that survey participation has ended. If eligible, respondents are allowed to continue survey participation.

The electronic data capture (EDC) system that is used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient-identifying information will be stored separately from survey data.

6.1.1 Telephone

The telephone survey is facilitated by a trained interviewer from the Survey Coordinating Center using a CATI program. The respondent will be required to provide a unique code to access the survey. Working from a CATI script, the interviewer will read questions or statements to the respondent and enter the responses into the EDC system. Screening and main elements of the questionnaire will be administered sequentially during the same telephone call. Telephone interviewing allows participation of respondents who do not have Internet access, or prefer to complete the survey in this manner.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If respondents select to participate in the survey online, they will be directed to a secured website and instructed to enter a unique code to access the survey. An Internet survey will be

convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer interviews.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. Any free text fields will be grouped into applicable categories. Verbatim text from open-ended questions will be displayed when appropriate. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed all questions presented to them~~the survey~~
- Description of survey participants, including:
  - Type of respondent (patient/caregiver)
  - Age (patient/caregiver)
  - Gender (respondent)
  - Educational level (respondent)
  - Main language spoken at home (respondent)

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- Ethnicity (respondent)
- Race (respondent)
- Geographic region (respondent)

- Data from all respondents who completed all questions presented to them in the survey ("completers") will be analyzed, including:
- Frequency distribution of responses to each key risk message question. (the number of respondents who give each answer to each question)
- Percent of completersrespondents selecting desired response to each question relating to each key risk message and 95% CI.

Measurement of understanding will be computed for each question of the key risk message individually. A secondary analysis will be conducted to determine the number of completersrespondents who answered all items correctly for the key risk message. Behavior questions will be summarized on a question-by-question basis and are not included in the analysis by key risk message.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The survey will be conducted via the Internet and by telephone. It is possible that a respondent may report an adverse event or other safety event experienced while taking TIRF medicines either in free text fields of the survey or while in conversation with the Survey Coordinating Center. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. The respondent will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact him/her if there are questions about the survey. The Internet-based questionnaires will be monitored for any comments recorded in free text fields. Information on all comments that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE/PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE/PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail a $5025 gift card, a Thank You Letter, a product-specific Medication Guide, and correct survey responses to key risk message questions after the survey is completed. Respondent contact information is also requested in the event a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information. A respondent may be contacted only if clarification or follow-up is needed regarding a possible safety event that was mentioned to the interviewer or recorded in free text fields of the online survey.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to receive TIRF medicines.

This protocol and survey will be reviewed and approved by a central Institutional Review Board (IRB) before administration of the survey.

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APPENDIX A Screening and Main Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets. **[PATIENT]** indicates text applicable to a patient when it differs from survey text for caregivers, parents and legal guardians. **[PARENT/CAREGIVER/LEGAL GUARDIAN]** indicates text applicable to parents, caregivers, and legal guardians when it differs from survey text for patients.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by tlelphone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as “I don’t know,” “Prefer not to answer” or “None of the above” will always appear at the end of the randomized responses.

- **[GO TO Ax]** (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

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Survey Legend

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

  Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

  Northeast Region
  - New England Division - ME, NH, VT, MA, RI, CT
  - Middle Atlantic Division - NY, NJ, PA

  Midwest Region
  - East North Central Division - OH, IN, IL, MI, WI
  - West North Central Division - MN, IA, MO, ND, SD, NE, KS

  South Region
  - South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
  - East South Central Division - KY, TN, AL, MS
  - West South Central Division - AR, LA, OK, TX

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Survey Legend

West
- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN ~~ONLINE/PHONE~~ SURVEY CONTENT]

~~**[PREAMBLE 1]**~~

~~Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are **T**ransmucosal **I**mmediate **R**elease **F**entanyl medicines, also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** (and sometimes called "fast acting fentanyls") or TIRF medicines.~~

~~**(INTERVIEWER: Pronounce "TIRF," then spell out T-I-R-F).**~~

~~The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.~~

~~There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.~~

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are **T**ransmucosal **I**mmediate **R**elease **F**entanyl medicines, also known as rapid onset opioids (and sometimes called "fast acting fentanyls") or TIRF medicines.

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

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~~ONLY]~~How We Use Your Information

~~[PHONE ONLY] Now I would like to tell you about how your contact information will be used.~~

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $5025 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

~~[ONLINE ONLY]~~ How We Protect Your Privacy

~~[PHONE ONLY]Now I would like to tell you about how we protect your privacy.~~

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB). Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

~~[ONLINE ONLY]~~ How to Learn More About This Survey~~Transmucosal Immediate Release Fentanyl Medicines~~

~~[ONLINE ONLY]~~ If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297.

Once you have answered a question and moved on, you cannot go back and change your answers.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4). ~~[PHONE ONLY] Please feel free to ask me to repeat any questions or statements as we go through the survey.~~

~~Once you have answered a question and moved on, you cannot go back and change your answers.~~

Comment [24mos1]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

Comment [24mos2]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

Comment [24mos3]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

~~If you have questions about your rights as a research participant or related concerns, you may contact the IRB at~~ (b) (4) ~~.~~ **~~[ONLINE ONLY]~~** Be sure to write down this telephone number; it will not be displayed again.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands. These are **T**ransmucosal **I**mmediate **R**elease **F**entanyl medicines, also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** (and sometimes called "fast acting fentanyls") or TIRF medicines.

(INTERVIEWER: Pronounce "TIRF," then spell out T-I-R-F).

The information collected will help the makers of TIRF medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF medicines.

Now I would like to tell you about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be put together and reported in anonymous form to manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

Now I would like to tell you about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA (Food and Drug Administration) and a company called (b) (4)., which is the Institutional Review Board (IRB). Your choice to allow the manufacturers of TIRF medicines to use your information is entirely voluntary, but necessary to take part in this survey.

Please feel free to ask me to repeat any questions or statements as we go through the survey.

Once you have answered a question and moved on, you cannot go back and change your answers.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4).

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF medicines, talk to your doctor, pharmacist, or other health care professional.

Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

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1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 43 months, have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.

   - ○ Yes **[GO TO Q4]Q4]**
   - ○ No
   - ○ I don't know

3. Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 43 months? As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands.

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. **[PATIENT]** For which TIRF medicines have you filled a prescription in the last 4 months? Please select all that apply.

[CAREGIVER] For which TIRF medicines has the person you care for filled a prescription in the last 4 months? Please select all that apply.

- ☐ Abstral
- ☐ Actiq, including generic versions of Actiq
- ☐ Fentora
- ☐ Lazanda
- ☐ Onsolis
- ☐ Subsys
- ☐ Other
- ○ I don't know **[CLEAR ALL OTHER SELECTIONS]**

4.5. Have you ever taken part in a survey about a TIRF medicine before?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

5.6. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE]**
- ○ 18 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

6.7. **[CAREGIVER ONLY]** Which of the following groups best describes the patient's age?

- ○ Under 16
- ○ 16 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer

7.8. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- □ Anesta LLC **[TERMINATE]**
- □ Archimedes Pharma US Inc. **[TERMINATE]**
- □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**

- ☐ Endo Pharmaceuticals Inc. **[TERMINATE]**
- ☐ Galena Biopharma~~BioPharma~~ **[TERMINATE]**
- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt~~, the Pharmaceuticals business of Covidien~~ **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions~~SolutionsMeda Pharmaceuticals~~ **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ ProStrakan, Inc. **[TERMINATE]**
- ☐ RelayHealth**[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA (Food and Drug Administration) **[TERMINATE]**
- ☐ No **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**

[PREAMBLE 2]

[PATIENT]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for you. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[CAREGIVER]Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for the patient. TIRF medicines include Abstral®,

Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you or to the patient by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

8.9. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed to the patient? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of these brands.

- ○ Yes
- ○ No
- ○ I don't know

9.10. **[PATIENT]** For which of the following conditions should I use a TIRF medicine?

[CAREGIVER] For which of the following conditions should the person I take care of use a TIRF medicine?

[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
9a.10 Headache or migraine pain	○	○	○
9b.10 Breakthrough pain from cancer	○	○	○
9c.10 Dental pain	○	○	○
9d.10 Pain after surgery	○	○	○
9e.10 Long-lasting painful conditions not caused by cancer	○	○	○

10.11 Please answer True, False, or I don't know for the following statement:

TIRF medicines should only be taken by patients who are opioid tolerant.

- o True
- o False
- o I don't know

11.12 Please answer True, False, or I don't know for each of the following statements.

[RANDOMIZE LIST]	True	False	I don't know
11a.1 Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	o	o	o
11b.1 If a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.	o	o	o
11c.1 It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	o	o	o
11d.1 A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	o	o	o

12.13 **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	True	False	I don't know
12a.1 TIRF medicines should be stored in a safe place out of the reach of children.	o	o	o
12b.1 It is OK for patients to take TIRF medicines for headache pain.	o	o	o
12c.1 TIRF medicines should be taken exactly as prescribed by the doctor.	o	o	o
12d.1 TIRF medicines can cause life-threatening breathing problems that can lead to death.	o	o	o

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13.14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- o Wait an hour and see if the person is OK.
- o Get emergency help right away.
- o Do nothing.
- o I don't know

14.15 **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

15.16 **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

16.17 **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
16a.1 Selling or giving away TIRF medicines is against the law.	○	○	○
16b.1 It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
16c.1 TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
16d.1 TIRF medicines are only available to patients through a special program (called the TIRF REMS Access program).	○	○	○
16e.1 A TIRF medicine can cause an overdose and death in any child who takes it.	○	○	○

[PREAMBLE 3]

[PATIENT] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for the patient.

[BOTH] A Medication Guide is a paper handout that contains important information about the risks associated with the use of a TIRF medicine and how to use it safely. Medication Guides always include the title "Medication Guide" followed by the name of the medicine and its pronunciation. The Medication Guide usually has a section titled "What is the most important information I should know?" The Medication Guide is in a question-and-answer format and may be given to you by your pharmacist or doctor.

[END PREAMBLE 3]

17.18 **[PATIENT]** Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?

[CAREGIVER] Have you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for the patient?

- Yes
- No **[GO TO PREAMBLE 4]**
- I don't know **[GO TO PREAMBLE 4]**

18.19 **[PATIENT]** Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

[CAREGIVER] Did you or the patient receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

- Yes
- No **[GO TO Q21]~~Q20~~]**
- I don't know **[GO TO Q21]~~Q20~~]**

19.20 **[PATIENT]** When was the Medication Guide given to you? Please select all that apply.

[CAREGIVER] When was the Medication Guide given to you or the patient? Please select all that apply.

- At the first appointment with the doctor who prescribed the TIRF medicine
- At the last appointment with the doctor who prescribed the TIRF medicine
- I don't remember **[CLEAR ALL OTHER SELECTIONS]**

20.21 **[PATIENT]** Did you receive the Medication Guide for the TIRF medicine from the pharmacy?

[CAREGIVER] Did you or the patient receive the Medication Guide for the TIRF medicine from the pharmacy?

- ○ Yes
- ○ No **[GO TO Q23|~~Q22~~]**
- ○ I don't know **[GO TO Q23|~~Q22~~]**

21.22 **[PATIENT]** How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] How frequently do you or the patient receive a Medication Guide for the TIRF medicine at the pharmacy?

- ○ Only with the first filled prescription
- ○ Each time a prescription is filled
- ○ Other (please specify): _____
- ○ I don't know

22.23 Did you read the Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26|~~Q25~~]**
- ○ I don't know **[GO TO Q26|~~Q25~~]**

23.24 How much did you read?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ I don't know

24.25 How much of the Medication Guide did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

25.26 Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO Q30]~~Q29]~~**
- ○ I don't know **[GO TO Q30]~~Q29]~~**

26.27 Who offered to explain the Medication Guide to you? (Select all that apply.)

- □ The doctor or another healthcare professional in the doctor's office
- □ The pharmacist where the TIRF medicine prescription was filled
- □ Someone else (specify the type of person but not his/her name)

_____

27.28 Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO Q30]~~Q29]~~**
- ○ I don't know **[GO TO Q30]~~Q29]~~**

28.29 How much of the explanation did you understand?

- All of it
- Most of it
- Some of it
- None of it
- I don't know

29.30 Did you or do you have any questions about the information in the Medication Guide?

- Yes
- No **[GO TO PREAMBLE 4]**
- I don't know **[GO TO PREAMBLE 4]**

30.31 What are your questions? **[MULTILINE INPUT]**

[PREAMBLE 4]

The next set of questions is about the Patient-Prescriber Agreement Form for TIRF medicines. As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands. The Patient-Prescriber Agreement is a form that is signed by the doctor and the patient or their caregiver. This form may also be referred to as the Prescriber-Patient Agreement.

[END PREAMBLE 4]

31.32 Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- Yes
- No **[GO TO Q34]~~Q33]~~**
- I don't know **[GO TO Q34]~~Q33]~~**

~~32.~~33 How much of the explanation did you understand?

- All of it
- Most of it
- Some of it
- None of it
- I don't know

~~33.~~34. **[PATIENT]** Did you sign a Patient-Prescriber Agreement Form?

[CAREGIVER] Did you or the person you are caring for sign a Patient-Prescriber Agreement Form?

- Yes
- No **[GO TO DEMOGRAPHICS PREAMBLE]**
- I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

~~34.~~35. Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?

- Yes
- No
- I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

~~35.~~36 What is your gender?

- Male
- Female
- Prefer not to answer

36.37 What is the highest level of education you have completed?

- Less than high school
- Some high school
- High school graduate/GED
- Some college/Associate's degree
- Bachelor's degree
- Master's degree
- Professional or Doctoral degree
- Prefer not to answer

37.38 What is the main language you speak at home? (Please select only one.)

- English
- French
- Spanish
- Portuguese
- Italian
- German
- Chinese
- Japanese
- Korean
- Other
- Prefer not to answer

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38.39 Are you Hispanic or Latino?

- Yes
- No
- Prefer not to answer

39.40 For informational purposes only, which of the following U.S. census categories best describes your race? (Please select only one.)

- American Indian or Alaska Native
- Asian (origins of Far East, Southeast Asia or the Indian subcontinent)
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Other
- Prefer not to answer

40.41 In which state do you live?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

You are eligible to receive a $5025 gift card for your time completing the survey. In order to receive the gift card, we need to collect your name and address so that we can mail it to you. If you do not provide your name and address you will not receive the gift card for your time taking the survey.

41.42. Do you agree to give us your name and mailing address so we can send your payment?

- ○ Yes
- ○ No **[SKIP TO CLOSING 2]**

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

42.43. Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[CLOSING 3]

This is the end of the survey. If you have questions about the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Thank you again for your help.

[END OF SURVEY CONTENT]

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APPENDIX B Patient Letter of Invitation

[PAT_FIRST_NAME] [PAT_LAST_NAME
[CURR_DATE]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

Thank you for choosing [pharmacy partner or PBM name] for your prescription needs. The purpose of this letter is to inform you about a voluntary research survey being conducted by [COMPANY], the maker of [BRAND_GENERIC]. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about [BRAND] and other medicines like it. The first 300 people who complete this 20-minute survey and provide their contact information will receive a $5025 [pharmacy partner or PBM name] gift card from [COMPANY] to thank them for their time.

You may be eligible to take part if you have taken [BRAND] and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about [BRAND] and where you get your medical information.

If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

It is recommended that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

(over, please)

You are not required to take part in this survey. If you choose to take part, please be assured that your contact information and your individual responses will be kept strictly confidential. You will not be asked to identify yourself to participate in the survey. However, if you wish to receive the $5025 ~~25~~ gift card from [COMPANY], you must provide your name and contact information for delivery. Your answers to the survey questions will be combined with answers given by others, and your name will not be used in any written report or publication. Neither taking the survey nor your answers to the questions will affect your ability to receive or take [BRAND].

Sincerely,

[Pharmacy partner or PBM name]

[COMPANY] funded the cost of the gift card, the cost of mailing this letter and paid a fee to [pharmacy partner or PBM name]. The research study is not being conducted by [pharmacy partner or PBM name]. No information that can identify you, your medication, or your health condition will be provided by [pharmacy partner or PBM name] to [COMPANY]. This letter provides information about a drug prescribed by your doctor and is not a recommendation by [pharmacy partner or PBM name] to use a particular drug for your condition. Call [pharmacy partner or PBM name] toll free at xxx-xxx-xxxx if you do not wish to continue receiving mailings about [BRAND] from [pharmacy partner or PBM name].

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 2, 24-month REMS Assessment; Version 1.0
Survey Time Period	16 September 2013 – 16 October 2013
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics Mallinckrodt Pharmaceuticals Meda Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	18 December 2013

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
ANDA	Abbreviated New Drug Application
CSP	Closed System Pharmacy
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
KAB	Knowledge, Attitudes, and Behavior
NDA	New Drug Application
QR	Qualitative Research
REMS	Risk Evaluation and Mitigation Strategy
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

1. PHARMACIST SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and their generic equivalents. The TIRF Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics, Mallinckrodt Pharmaceuticals, Meda Pharmaceuticals, Mylan, Inc., and Par Pharmaceutical, Inc. At the time of protocol finalization for the Knowledge, Attitude, and Behavior (KAB) surveys, Depomed, Inc. acquired the New Drug Application (NDA) for Lazanda (29 July 2013) from Archimedes Pharma US, Inc., who is no longer a TIRF Sponsor. In addition, Galena Biopharma acquired the NDA for Abstral from Prostrakan, Inc. and is now a TIRF Sponsor (as of 01 May 2013) whereupon ProStrakan exited the group. Additionally, Mylan became a TIRF Sponsor on 29 May 2013 due to a pending Abbreviated New Drug Application (ANDA).

The Food and Drug Administration (FDA) has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on 28 December 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information of each product. The protocol describes the administration of these surveys among pharmacists who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

This report describes the results from the pharmacists survey conducted for the 24-month TIRF REMS Access Program Assessment. The 24-month KAB survey launched on 16 September 2013 and closed on 16 October 2013.

2. PHARMACIST SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey also collects data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions that were designed to test pharmacist understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Development: FDA Feedback and Qualitative Research of Draft Survey Questionnaire

On 12 March 2013, FDA provided feedback on the 12-month TIRF REMS Access Program Assessment Report that included recommendations for modifications to the pharmacist survey, as described below:

(1) Add the questions, identified below, as key risk messages in the 24-month TIRF REMS Access Program Assessment Report and investigate the cause for low scores to these questions specifically relating to the safe use questions that potentially indicate poor understanding of these concepts. *The following questions, identified by the FDA, were moved to key risk messages*.

12-month Survey Question Number	24-month Survey Question Number	Question
5	**5**	Please select True, False, or I don't know for each of the following. According to the labeling, patients considered opioid-tolerant are those:
5a	**5a**	Who are taking regular therapy for underlying persistent cancer pain for one week or longer
5b	**5b**	Who are not currently taking opioid therapy, but have taken opioid therapy before
5c	**5c**	Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl
8	**9**	For which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option
8e	**9e**	Chronic non-cancer pain

(2) Investigate the causes, including conducting a pre-testing of all questions related to key risk messages, prior to your next survey to determine the reasons for the poor performance on these questions. If your pre-testing indicates that a re-phrasing of a question is indicated, please also re-test the re-phrased question and then submit the results of both the pre-testing and re-testing.

Before implementing the 24-month survey, TRIG conducted a Qualitative Research (QR) interview of 7 items from the Pharmacist REMS Assessment Survey Questions and 1 new question that was not included in the 12-month survey, (see Appendix C). The research undertaken in this QR process included:

- Review of the questions identified by the FDA that had a low correct response rate;
- Review of 1 new question created to assist in the determining the understanding of the term "around-the-clock usage";
- Review of proposed new wording on various questions.

The objectives of this research were to:

- Evaluate clarity and comprehension of questions and answer options used in the 12-month assessment;
- Identify terms, questions or topics for clarification or revision based on any areas of confusion with or misunderstanding for current wording;
- Determine how participants understand specific questions and why those questions are answered a particular way;
- Determine how certain questions might be understood differently and answered more accurately if further clarified;
- Evaluate alternative language for these questions.

This QR involved in-depth, individual telephone interviews with 7 pharmacists. Each interview lasted about 45 minutes. All interviews were conducted by the same experienced moderator using a detailed discussion guide that probed into each area of the survey questions identified for further investigation. The strategy used to conduct the 7 telephone interviews was to interview:

- 7 TIRF REMS Access pharmacists who completed the 12-month Pharmacist REMS Assessment Survey and met the definition of a "low performer" based on their incorrect responses on 3 to 7 of the 10 items identified by FDA.

Based on the outcome of the QR, the following questions were added or reworded for Wave 2. A tracked-change version of the protocol can be found in Appendix D.

The following new questions were added to the 24-month REMS Assessment based on QR findings.

24-month Survey Question Number	Question
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.
6a	A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time
6b	A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain

The following questions were revised for the TIRF REMS KAB 24-month survey:

12-month Survey Question Number	12-month Question	24-month Survey Question Number	24-month Question
5	Please select "True", "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:	**5**	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:
5a	Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer	**5a**	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer
5c	Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	**5c**	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy
8	For which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Answer "Yes," "No," or "I don't know" for each option.	**9**	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option
8e	Chronic non-cancer pain	**9e**	Chronic non-cancer pain

After the initial review and subsequent to QR, the survey was updated and re-submitted to the FDA. On 01 August 2013, FDA provided feedback and the following revisions were made (see Appendix A and Appendix B) to the survey and protocol, as appropriate, to incorporate these requests:

- Include in analyses all eligible surveys that are completed.

This information was incorporated in the 12-month survey and in all subsequent surveys.

Appendix C includes a copy of the Top-Line Findings Report: Findings Report: Qualitative Research to Evaluate the Prescriber and Pharmacist 12-month REMS Assessment Surveys for TIRF Medicines.

3.2 Survey Sample

This survey was conducted among a random sample of pharmacists who were enrolled in the TIRF REMS Access Program as of 15 August 2013. A target sample of 300 pharmacists who dispense TIRF products and were known to have received the REMS educational materials were surveyed in this second KAB survey conducted from 16 September 2013 to 16 October 2013. The size of the sample was determined based on both practical and statistical considerations.

3.2.1 Eligibility

Subject recruitment was from a random sample of pharmacists from pharmacies that were enrolled in the TIRF REMS Access Program. (The number of pharmacies enrolled in TIRF REMS Access Program on 10 October 2013 is provided in Table 4). Any pharmacist who worked at an enrolled pharmacy was eligible to participate. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation (UBC), or the FDA were not eligible to participate.

Respondents who participated in the first wave of the TIRF KAB survey (12-month TIRF REMS Access Program Assessment) were not eligible to participate.

3.2.2 Recruitment

Subject recruitment was performed via a letter sent through the United States Postal Service (USPS), and via fax (see Section 5.1.1 for more detail).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; second and third mailings were sent to non-respondents from the original sample to maximize participation. At the end of the 3rd mailing, the pharmacists had not reached the survey sample target; therefore, a new random sample was selected and invitations were mailed through the USPS or faxed.

Each letter of invitation included a unique code needed to complete the survey. There were three categories of pharmacies which were Closed System Pharmacy (CSP), Inpatient Pharmacy and Outpatient Pharmacy. Each type of pharmacy was provided with a unique access code in order to determine which questions were displayed. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed).

Pharmacists were given the option of taking the survey by telephone via the Survey Coordinating Center or online via a secure website. All participating pharmacists were offered an honorarium of $50 for a completed survey. The survey was estimated to take approximately 20 minutes to complete.

3.3 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the pharmacists' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

3.3.1 Key Risk Message 1

Key Risk Message 1 referred to the pharmacist's knowledge of the specific contraindications for TIRF medicines in opioid non-tolerant patients. Questions in **bold face type** were added as key risk message questions based on FDA feedback.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	**Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:**	
5a	**Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer**	***True***
5b	**Who are not currently taking opioid therapy, but have taken opioid therapy before**	***False***
5c	**Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy**	***False***

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used in opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***

3.3.2 Key Risk Message 2

Key Risk Message 2 referred to the pharmacist's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients. Question 9e, identified in **bold face type,** was added as a key risk message question based on FDA feedback.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	**Chronic non-cancer pain**	***No***

3.3.3 Key Risk Message 3

Key Risk Message 3 referred to the pharmacist's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Key Risk Message 3: **TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.**		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement about TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
10	Please answer True, False, or I don't know for each statement about TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***

3.3.4 Key Risk Message 4

Key Risk Message 4 referred to the pharmacist's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement about TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***

3.4 Additional Questions

The survey also contained questions (Question 12a-f) about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials. The following questions about behaviors were asked after the key risk message questions:

Question No.	Question
12	How frequently do you perform the following activities when dispensing TIRF medicines?
12a	Ask patients (or their caregivers) about the presence of children in the home
12b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
12c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
12d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
12e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
12f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible pharmacists who completed the survey. Eligible pharmacists were defined as those respondents who answered ***Yes*** to Question 1 (agree to take part in survey), and Question 3 (work at a pharmacy that is enrolled in the TIRF REMs Access Program), and ***No*** to Question 2 (participated in past survey) and Question 4 (worked for a TRIG company, UBC, or FDA). A completed survey was a survey in which all non-eligibility questions as appropriate were answered. Some questions may not have been answered because of skip logic in the survey questionnaire.

4.1.2 Sub-populations of Interest

The following sub-group analyses were conducted if the sub-group included at least 20 respondents. Of note, sub-group analysis 3 was not done since only 9 pharmacists completed the survey via telephone.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 18, 19, 20 and 21):

- S-1a - Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).
- S-1b - Respondents who responded No or I don't know to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.

Sub-group analysis 2: Time to complete survey - Internet:

- S-2a - <10 min
- S-2b - 10 to <20 min
- S-2c - ≥20 min

Sub-group analysis 3: Time to complete survey - Telephone:

- S-3a - <10 min
- S-3b - 10 to <20 min
- S-3c - ≥20 min

Sub-group analysis 4: Modality to complete survey:

- S-4a - Internet
- S-4b – Telephone

Sub-group analysis 5: Time practicing as a pharmacist (Question 28):

- S-5a - Less than 3 years
- S-5b - 3 to 5 years
- S-5c - 6 to 15 years
- S-5d - More than 15 years

Sub-group analysis 6: Number of times per month dispensed TIRF medicines within the last 6 months (Question 25):

- S-6a - None
- S-6b - 1 - 2 times per month
- S-6c - 3 - 5 times per month
- S-6d - More than 5 times per month

Results of sub-group analyses performed are provided in Appendix B: Tables 6.1 and 6.2, 7.1 and 7.2, 8.1 and 8.2, 9.1 and 9.2.

4.1.2.1 Primary Analyses

Primary analyses were done for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/item defined by the key risk message. The correct response to each question/item was identified in the body of the risk message table (Section 3.3).

4.1.2.2 Secondary Analyses

Secondary analyses evaluated the number and percentages of correct responses and the average number of correct responses within the risk message overall to assess understanding of the comprehensive key risk message. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message.

4.1.3 Pharmacist Report of Adverse Event, Product Complaint, or Medical Information Request During Survey

A pharmacist may have reported an adverse event or other event experienced by their patients while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the Survey Coordinating Center Associate. If the event was mentioned to an Associate, the Associate documented the event or complaint, the verbatim response, and the pharmacist's contact information, if provided. The pharmacist was also informed that a representative from the appropriate TIRF medicine manufacturer may contact them to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine manufacturer for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the pharmacist responses to questions in the KAB survey are summarized in this section and a full set of responses can be found in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 7167 pharmacists were invited to participate in this survey (Table 1). Of those invited to participate, 5,982 were outpatient pharmacists, 860 were inpatient pharmacists, and 325 were pharmacists practicing in CSPs. Some pharmacists received more than 1 reminder.

From the total 403 respondents, 300 pharmacists met eligibility criteria and completed the survey. Of these 300 pharmacists, 291 (97.0%) completed the survey online, and 9 (3.0%) completed it by telephone (Table 3). Of the 300 pharmacists who completed the survey, 4 were CSP pharmacists, 15 were inpatient pharmacists, and 281 were outpatient pharmacists.

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Pharmacists N=372[1]	
	All Respondents	
	N	%
Number of invitations issued to pharmacists	7167	
Number of reminder letters issued to pharmacists	13215	
Number of pharmacists screened for participation	372[1]	
Number of pharmacists eligible for participation	300	
Number of screened pharmacists eligible for participation who answered all questions presented to them	300	80.6[1]
Method of Survey Completion		
Number of surveys completed by telephone	9	3.0[2]
Number of surveys completed by Internet	291	97.0[2]

[1] The denominator for the percentage of eligible pharmacists is the number of screened pharmacists (N=372).
[2] The denominator for percentages completed by telephone or Internet is the number of eligible pharmacists who completed the survey. (N=300).

As shown in Table 2, a total of 371 pharmacists agreed to participate in this survey, 339 of these pharmacists stated they had not taken part in the survey about TIRF medicines before, and 304 of these pharmacists worked in pharmacies that were enrolled in the TIRF REMS. Of the 372 total respondents, 68 were ineligible to participate in the survey because they either did not agree to participate, indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before, or worked in pharmacies that were not enrolled or they did not know whether their pharmacy was enrolled in the TIRF REMS. Of the 304 respondents who reported that their pharmacies were enrolled in the TIRF REMS Access Program, 1 respondent was ineligible for the survey because the respondent, or an immediate family member, had worked for a TRIG company in the past, 1 was ineligible because the respondent or an immediate family member, had worked for the FDA in the past, and 2 respondents preferred not to answer the question.

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists N=372		Eligible Completed Pharmacists N=300	
	n	%	n	%
Question 1: Do you agree to participate in this survey?				
Yes	371	99.7	300	100.0
No[1]	1	0.3		
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and generic versions of any of these brands				
Yes[1]	8	2.2		
No	339	91.1	300	100.0
I don't know[1]	24	6.5		
Question not asked[2]	1	0.3		
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?				
Yes	304	81.7	300	100.0
No[1]	8	2.2		
I don't know[1]	27	7.3		
Question not asked[2]	33	8.9		
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]				
Anesta LLC.[1]	0	0.0		
Archimedes Pharma US Inc.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	0	0.0		
Endo Pharmaceuticals Inc.[1]	1	0.3		
Galena Biopharma[1]	0	0.0		
Insys Therapeutics[1]	0	0.0		
Mallinckrodt[1]	0	0.0		
McKesson Specialty Care Solutions[1]	0	0.0		
Meda Pharmaceuticals[1]	0	0.0		
Mylan Inc.[1]	0	0.0		

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists N=372		Eligible Completed Pharmacists N=300	
	n	%	n	%
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
RelayHealth[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	0	0.0		
United BioSource Corporation[1]	0	0.0		
FDA[1]	1	0.3		
None of these apply[4]	300	80.6	300	100.0
I don't know[1]	0	0.0		
Prefer not to answer[1]	2	0.5		
Question not asked[2]	68	18.3		

[1] Ineligible to participate in the survey.
[2] Question not asked due to a previous question elimination.
[3] More than 1 response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Those taking the survey online took an average of 14.3 minutes to complete it, while those taking it by telephone took an average of 18.0 minutes.

Table 3. Time to Complete Survey for Completers (Minutes)

Summary Statistic	Telephone	Internet	Total[1]
N	9	291	300
Mean (± SD)	18.0 (1.81)	14.3 (8.75)	14.4 (8.64)
Minimum	15	4	4
Median	18.0	11.6	11.8
Maximum	20	85	85
Category			
0 – <5 Minutes	0	1	1
5 – <10 Minutes	0	90	90
10 – <15 Minutes	0	106	106
15 – <20 Minutes	8	47	55
20 – <25 Minutes	1	21	22

Table 3. Time to Complete Survey for Completers (Minutes)

Category			
25 – <30 Minutes	0	12	12
30 Minutes or More	0	14	14

[1] Number of eligible pharmacists completing the survey (See Table 1).

5.1.2 Pharmacist Demographic and TIRF Product Dispensing Characteristics

The demographic characteristics of pharmacists who completed the survey are shown in Table 4, and their experience with prescribing TIRF medicines is summarized in Table 5.

The majority of pharmacists who completed the survey were male (183, 61.0%), and out of 300 eligible pharmacists, 157 (52.3%) had been a practicing pharmacist for more than 15 years. Respondents from the South, Northeast, and Midwest reflected 32.3%, 26.0%, and 24.0% of total respondents, respectively, while respondents from the Western region of the United States (US) composed 17.3% of total respondents. The proportion of respondents who completed the survey within each geographic region was similar to the overall proportion of pharmacies enrolled in the TIRF REMS Access Program as of 10 October 2013 in each geographic region (Table 4). There were no respondents from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam identified as "Other" in Table 4 below.

Most pharmacists (242, 80.7%) functioned as the pharmacist-in-charge for the TIRF REMS Access Program where they worked, and a majority of pharmacists (235, 78.3%) had dispensed a TIRF medicine zero to 2 times per month within the past 6 months. The most frequently dispensed TIRF medicine within the 6 months prior to taking the survey was Actiq or generic Actiq (120 pharmacists, 77.4%).

Table 4. Demographic Characteristics of Eligible Pharmacists

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 27: What is your gender?		
Male	183	61.0
Female	111	37.0
Prefer not to answer	6	2.0
Question 28: In total, how many years have you been a practicing pharmacist		
Less than 3 years	23	7.7
3-5 years	41	13.7
6-10 years	40	13.3

Table 4. Demographic Characteristics of Eligible Pharmacists

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
11-15 years	34	11.3
More than 15 years	157	52.3
Prefer not to answer	5	1.7
Question 29: In which state do you practice?[2]		

Geographic Region[2]	Eligible and Complete Respondents N=300		Pharmacies Enrolled in TIRF REMS Access Program as of 10Oct2013 by Region N=38,597	
	N	%	N	%
Northeast	78	26.0	7834	20.3
Midwest	72	24.0	8027	20.8
South	97	32.3	15027	38.9
West	52	17.3	7549	19.6
Other	0	0.0	160	0.4
Prefer not to answer	1	0.3	0	0.0

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] According to the 2001 Geographic Area Regions set by the US Census Bureau, Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

Table 5. Characteristics of Respondents Completing the Survey

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 24: Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?		
Yes	242	80.7
No	52	17.3
I don't know	6	2.0
Question 25: On average, how many times per month have you dispensed TIRF medicines within the last 6 months		
None	145	48.3
1-2 times per month	90	30.0
3-5 times per month	32	10.7
More than 5 times per month	15	5.0
I don't remember	18	6.0
Question 26: Please select the TIRF medicine(s) that you have dispensed within the last 6 months (select all that apply):[2]		
Abstral®	8	5.2
Actiq® or generic Actiq	120	77.4
Fentora®	57	36.8
Lazanda®	6	3.9
Onsolis®	1	0.6
Subsys®	17	11.0
N/A (answered None to Question 25)	145	

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question, which may not reflect the entire sample because of skip logic in the survey.

N/A = Not applicable.

5.1.3 TIRF Medicines Educational Materials

Pharmacists were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide (Table 6). Almost all pharmacists reported they had received or had access to the Full Prescribing Information and the Medication Guide (291, 97.0%; and 297, 99.0%, respectively). Of those with access to these materials, 76.6% and 84.2%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide.

Table 6. Responses to Questions About TIRF Medicines Educational Materials

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 18: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?		
Yes	291	97.0
No	1	0.3
I don't know	8	2.7
Question 19: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?[2]		
Yes	223	76.6
No	61	21.0
I don't know	7	2.4
N/A (answered ***No*** or ***I don't know*** to Question 18)	9	
Question 20: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?		
Yes	297	99.0
No	1	0.3
I don't know	2	0.7
Question 21: Did you read the Medication Guide for the TIRF medicine(s) that you dispense?[2]		
Yes	250	84.2
No	39	13.1
I don't know	8	2.7
N/A (answered ***No*** or ***I don't know*** to Question 20)	3	

Table 6. Responses to Questions About TIRF Medicines Educational Materials

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 22: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[3]	21	7.0
No	259	86.3
I don't know	20	6.7

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question, which may not reflect the entire sample because of skip logic in the survey.

[3] Verbatim text for questions about the information in the Full Prescribing Information are presented in Appendix B, Listing 2.

There were 18 respondents (6.0%) who typed a response into the free text field for Question 22 (*Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?)*. These responses are shown in Appendix B, Listing 2. Of the 18 responses, 13 were requests for medical information and 5 were indications the free text field was not applicable or they had no questions.

5.2 KAB Survey Objectives

5.2.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total eligible respondent population that completed the survey. A summary of results by sub-group is provided in a separate section of the document, Section 5.2.3.

5.2.1.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines.

Analysis of responses to components of Question 5 for Key Risk Message 1 showed that a high percentage of pharmacists knew that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer (271, 90.3%), and are those who are currently taking opioid therapy (242, 80.7%). Somewhat less understood was cancer patients with no known contraindications to the drug fentanyl, but who are not taking around-the-clock opioid therapy are not considered opioid tolerant (228, 76.0%). Further discussion is provided in Section 6.

Analysis of responses to components of Question 7 for Key Risk Message 1 showed that a high percentage of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients (86.0%) and that death has occurred in opioid non-tolerant patients treated

with some fentanyl products (93.7%). Similarly, 248 (82.7%) pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product, and that TIRF medicines may not be used to treat opioid non-tolerant patients (82.0%), (Table 7). Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 5.9 out of a possible 7.

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer		
True[2]	271	90.3 (86.4, 93.4)
False	23	7.7
I don't know	6	2.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	41	13.7
False[2]	242	80.7 (75.7, 85.0)
I don't know	17	5.7
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	52	17.3
False[2]	228	76.0 (70.8, 80.7)
I don't know	20	6.7

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	258	86.0 (81.6, 89.7)
False	27	9.0
I don't know	15	5.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	281	93.7 (90.3, 96.1)
False	2	0.7
I don't know	17	5.7
7c: TIRF medicines may be used in opioid non-tolerant patients.[4]		
True	40	13.3
False[2]	246	82.0 (77.2, 86.2)
I don't know	14	4.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	248	82.7 (77.9, 86.8)
False	38	12.7
I don't know	14	4.7
Secondary Analysis: Demonstrated Understanding		
0 correct responses	2	0.7
1 correct response	2	0.7

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
2 correct responses	6	2.0
3 correct responses	7	2.3
4 correct responses	22	7.3
5 correct responses	45	15.0
6 correct responses	86	28.7
7 correct responses	130	43.3
Average number of correct responses	5.9	(5.7, 7.0)[5]

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] Question 7c was presented to pharmacists participating in the internet survey as follows: TIRF medicines may be used in treat opioid non-tolerant patients. The word "treat" was included in error and was removed for reporting purposes.

[5] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.2 Key Risk Message 2

Key Risk Message 2 refers to the pharmacist's knowledge of the approved indications for prescribing TIRF medicines to opioid tolerant patients.

Responses to components of Question 9 for Key Risk Message 2 indicate that 268 (89.3%) pharmacists were aware that TIRF medicines are indicated for opioid-tolerant patients with breakthrough pain from cancer and not for patients with acute or postoperative pain (84.7%), headache or migraine pain (92.3%), or dental pain (96.7%), (Table 8). For Question 9e, only 47.0% of pharmacists correctly responded that TIRF medicines are not indicated for chronic non-cancer pain. Further discussion is provided in Section 6.

Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 4.1 out of a possible 5.

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	31	10.3
No[2]	254	84.7 (80.1, 88.6)
I don't know	15	5.0
9b: Headache or migraine pain		
Yes	8	2.7
No[2]	277	92.3 (88.7, 95.1)
I don't know	15	5.0
9c: Dental pain		
Yes	3	1.0
No[2]	290	96.7 (94.0, 98.4)
I don't know	7	2.3
9d: Breakthrough pain from cancer		
Yes[2]	268	89.3 (85.3, 92.6)
No	27	9.0
I don't know	5	1.7

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
9e: Chronic non-cancer pain		
Yes	126	42.0
No[2]	141	47.0 (41.2, 52.8)
I don't know	33	11.0
Secondary Analysis: Demonstrated Understanding		
0 correct responses	2	0.7
1 correct response	4	1.3
2 correct responses	12	4.0
3 correct responses	47	15.7
4 correct responses	114	38.0
5 correct responses	121	40.3
Average number of correct responses	4.1	(3.9, 5.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.3 Key Risk Message 3

Key Risk Message 3 refers to the pharmacist's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Responses to components of Questions 7, 8, and 10 for Key Risk Message 3 showed that 290 (96.7%) pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines; a personal history of past or current alcohol or drug abuse or family history of drug and alcohol abuse is a risk factor for opioid abuse (99.0%); and TIRF medicines can be abused in a manner similar to other opioid agonists (94.0%). Somewhat less understood was that a personal history of psychiatric illness is a risk

factor for opioid abuse (72.0%), (Table 9). Further discussion is provided in Section 6. Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 3.6 out of a possible 4.

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	290	96.7 (94.0, 98.4)
False	5	1.7
I don't know	5	1.7
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	216	72.0 (66.6, 77.0)
No	48	16.0
I don't know	36	12.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	297	99.0 (97.1, 99.8)
No	0	0.0
I don't know	3	1.0
Question 10: Please answer True, False, or I don't know for each statement about TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	282	94.0 (90.7, 96.4)
False	10	3.3

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
I don't know	8	2.7
Secondary Analysis: Demonstrated Understanding		
0 correct responses	0	0.0
1 correct response	3	1.0
2 correct responses	7	2.3
3 correct responses	92	30.7
4 correct responses	198	66.0
Average number of correct responses	3.6	(3.4, 4.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.4 Key Risk Message 4

Key Risk Message 4 refers to the pharmacist's knowledge that TIRF medicines are not interchangeable regardless of the route of administration.

Responses to components of Question 10b, c, and d for Key Risk Message 4 showed that 284 pharmacists understood TIRF medicines are not interchangeable with each other regardless of the route of administration (94.7%); the conversion of 1 TIRF medicine to another may result in a fatal overdose (92.0%); and dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (91.3%), (Table 10). Overall, evidence of understanding of this key risk information is further supported by the average number of correct responses identified as 2.8 out of a possible 3.

Table 10. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration.

Question	Eligible Completed Pharmacists N=300[1]	
	n	% (95% CI)[3]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	6	2.0
False[2]	284	94.7 (91.5, 96.9)
I don't know	10	3.3
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	276	92.0 (88.3, 94.8)
False	5	1.7
I don't know	19	6.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	274	91.3 (87.6, 94.3)
False	10	3.3
I don't know	16	5.3
Secondary Analysis: Demonstrated Understanding		
0 correct responses	5	1.7
1 correct response	11	3.7
2 correct responses	29	9.7
3 correct responses	255	85.0
Average number of correct responses	2.8	(2.6, 3.0)[4]

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.2 Other Survey Questions

5.2.2.1 Additional Questions About TIRF Medicines Safety

Table 11 summarizes the pharmacists' responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. Responses to these additional questions generally confirmed the pharmacists' understanding of the safety issues and the risks associated with taking TIRF medicines.

Question 6 (see Table 11) was added for this 24-month KAB survey to assist in determining the pharmacist understanding of around-the-clock usage, and 65.3% of pharmacists correctly indicated that a cancer patients should not be started on a TIRF medicine and an around-the-clock opioid at the same time, and 74.7% understood a cancer patient who had been on an around-the-clock opioid for 1 day should not start taking a TIRF medicine for breakthrough pain. Overall, greater than 70% of pharmacists correctly identified an opioid drug/dose regimen that, when taken by the patient, identifies patients as opioid tolerant according to the labeling for TIRF medicines. However, fewer understood that an equianalgesic dose of another oral opioid could also meet the definition of opioid tolerant (correct response 59.0%; Table 11). Pharmacists correctly indicated that TIRF medicines may not be sold, loaned, or transferred to another pharmacy (91.3%); pharmacy staff who dispense TIRF medicines must be educated on the requirements of the TIRF REMS Access Program (94.0%); and that TIRF medicines with the same route of administration cannot be substituted with each other (96.3%).

Thirteen (86.7%) inpatient pharmacists correctly indicated that it is not OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for home use (Table 12).

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.[2]		
6a: A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.		
True	80	26.7
False[3]	196	65.3
I don't know	24	8.0

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
6b: A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
True	50	16.7
False[3]	224	74.7
I don't know	26	8.7
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8c: A family history of asthma		
Yes	38	12.7
No[3]	245	81.7
I don't know	17	5.7
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[3]	237	79.0
False	29	9.7
I don't know	34	11.3
11b: 60 mg oral morphine/day		
True[3]	255	85.0
False	14	4.7
I don't know	31	10.3
11c: 30 mg oral oxycodone/day		
True[3]	214	71.3
False	44	14.7
I don't know	42	14.0

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
11d: 25 mcg transdermal fentanyl/hour		
True[3]	216	72.0
False	45	15.0
I don't know	39	13.0
11e: 25 mg oral oxymorphone/day		
True[3]	213	71.0
False	29	9.7
I don't know	58	19.3
11f: An equianalgesic dose of another oral opioid		
True[3]	177	59.0
False	61	20.3
I don't know	62	20.7
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.		
13a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.		
True	8	2.7
False[3]	274	91.3
I don't know	18	6.0
13b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.		
True[3]	282	94.0
False	6	2.0
I don't know	12	4.0

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.		
True	6	2.0
False[3]	289	96.3
I don't know	5	1.7

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Question 6 was presented to pharmacists participating in the internet survey as follows: Please answer True, False, or I don't know for each statement based on the labeling TIRF medicines. The word "for" was excluded in error and was added for reporting purposes

[3] Indicates the correct response(s) to each question or item within a question.

Table 12. Responses to Additional Questions About the Safe Use of TIRF Medicines: Question asked of Inpatient Pharmacists, Only

Question	Eligible Completed Pharmacists N=15[1]	
	n	%
Question 17: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient pharmacists, only)		
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.[3]		
True	0	0.0
False[2]	13	86.7
I don't know	2	13.3

[1] Question asked of inpatient pharmacists only.

[2] Indicates the correct response(s) to each question or item within a question.

[3] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

5.2.2.2 Pharmacist Activities When Dispensing TIRF Medicines

Pharmacists were asked about specific activities performed when dispensing TIRF medicines (Table 13).

Of the 300 eligible pharmacists, 167 (55.7%) responded they always ask their patients (or a patient's caregiver) about the presence of children in the home; 18.0% responded that they

ask only with the first prescription. Additionally, 69.3% responded they always instruct the patient (or their caregivers) not to share TIRF medicines, 66.0% responded they always counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal, 74.3% responded they always instruct patients (or their caregivers) to keep TIRF medicines out of reach of children, 66.0% responded they always instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines, and 91.3% responded they always give patients (or their caregivers) the Medication Guide for TIRF medicine.

Table 13. Responses to All Questions About Activities When Dispensing TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.		
12a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	167	55.7
Only with the first prescription	54	18.0
Sometimes	54	18.0
Never	13	4.3
I don't know	12	4.0
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	208	69.3
Only with the first prescription	52	17.3
Sometimes	26	8.7
Never	8	2.7
I don't know	6	2.0
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	198	66.0
Only with the first prescription	57	19.0
Sometimes	29	9.7
Never	8	2.7
I don't know	8	2.7

Table 13. Responses to All Questions About Activities When Dispensing TIRF Medicines

Question	Eligible Completed Pharmacists N=300[1]	
	n	%
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	223	74.3
Only with the first prescription	44	14.7
Sometimes	23	7.7
Never	5	1.7
I don't know	5	1.7
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	198	66.0
Only with the first prescription	67	22.3
Sometimes	26	8.7
Never	4	1.3
I don't know	5	1.7
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	274	91.3
Only with the first prescription	11	3.7
Sometimes	10	3.3
Never	0	0.0
I don't know	5	1.7

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

Specific pharmacy types (inpatient, outpatient, and CSP pharmacies) were each asked a single different question regarding pharmacy systems and processes. Question 14 was presented only to pharmacy respondents from inpatient pharmacies (N=15) as identified through the access code entered by the respondent (Table 14). Of the 15 respondents, 8 (53.3%) reported their pharmacy has processes to ensure compliance with the TIRF REMS Access Program requirements.

Table 14. Responses to All Questions About Activities When Dispensing TIRF Medicines: Asked of Inpatient Pharmacies Only

Question	Eligible Completed Inpatient Pharmacists N=15[1]	
	n	%
Question 14: Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program? [Inpatient pharmacists only][2]		
Yes	8	53.3
No	4	26.7
I don't know	3	20.0

[1] Number of eligible inpatient pharmacists completing the survey.
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of inpatient pharmacists to whom this question was presented.

Question 15 was presented only to pharmacy respondents from outpatient pharmacies (n=281) as identified through the access code entered by the respondent. This sub-population did not include respondents from CSPs (Table 15). Of the 281 respondents, 231 (82.2%) reported their pharmacy processes prescriptions for TIRF medicines through their pharmacy management system.

Table 15. Responses to All Questions About Activities When Dispensing TIRF Medicines: Outpatient Pharmacists Only

Question	Eligible Completed Outpatient Pharmacists N=281[1]	
	n	%
Question 15: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? [Outpatient pharmacists only][2]		
Yes	231	82.2
No	5	1.8
I don't know	45	16.0

[1] Number of eligible outpatient pharmacists completing the survey.
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of outpatient pharmacists to whom this question was presented.

Question 16 was presented only to pharmacy respondents from CSPs (N=4) as identified through the access code entered by the respondent (Table 16). Of the 4 respondents, 2 (50.0%) reported their pharmacy processes all prescriptions for TIRF medicines through the TIRF REMS Access Call Center.

Table 16. Responses to All Questions About Activities When Dispensing TIRF Medicines: Closed System Pharmacy Outpatient Pharmacists Only

Question	Eligible Completed CSP Pharmacists N=4[1]	
	n	%
Question 16: Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center? [CSP Outpatient pharmacists only][2]		
Yes	2	50.0
No	0	0.0
I don't know	2	50.0

[1] Number of eligible CSP outpatient pharmacists completing the survey.
[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of CSP pharmacists to whom this question was presented.

5.2.3 Analyses of Sub-populations

To further assess pharmacist understanding of key risk messages, sub-group analyses as described in Section 4.1.2 were conducted. Sub-group analysis of time to complete the survey for telephone respondents was not done since there were less than 20 respondents in this sub-group (telephone respondents; n=9). For the remaining sub-group analyses that were performed, all results are similar to the results in the primary analysis population, and no trends are evident. The full set of sub-group analysis tables is provided in Appendix B.

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N=300, Table 1), there were no adverse events or product complaints reported. In the Internet survey, respondents had the option to write in any questions they had when asked "*What are your questions*?" This prompt resulted in 18 individual responses by various completers, of which 13 were requests for medical information and 5 were indications that the free text field was not applicable or they had no questions (Appendix B, Listing 1). Since only medical information requests were received, the same information is reported in Appendix B, Listing 2 (qquestions about the information in the Full Prescribing Information or Medication Guide) as described in Section 5.1.3.

6. DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

The specific goal of the TIRF REMS pharmacist KAB survey was to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients.

Based on FDA feedback from the 12-month assessment, revisions were made to the 24-month pharmacist survey. As presented in Table 17 for changes in key risk message questions, there was a substantial improvement in correct response rate for key risk messages in the 24-month KAB survey compared with the 12-month KAB survey. Additionally, there was improvement in this 24-month KAB survey for Question 8a; this question was also included in Key Risk Message 3 in the 12-month KAB survey. A potential reason for the low performance on the 12-month assessment may be due to the short period of time that the shared system REMS was live prior to the 12-month survey (6 months). Prior to the 24-month survey, the questions were revised based on the QR results to improve understanding of the questions/items being tested. In addition, there were 22,762 (59%) pharmacies that enrolled or re-enrolled during this reporting period by successfully completing the education program, thereby reinforcing the educational message of the shared system REMS.

Table 17. Correct Response Rate in the 24-month KAB Survey Compared with the 12-month KAB Survey in Key Risk Message Questions Modified Between the Two Versions

12-month Survey Question Number	24-month Survey Question Number	Question as Presented in the 24-month Survey	12-month Survey Correct Response (%)	24-month Survey % Correct Response (%)
5	5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a	5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (***Correct Response True***)	12.6	90.3
5c	5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (***Correct Response False***)	15.6	76.0

Table 17. Correct Response Rate in the 24-month KAB Survey Compared with the 12-month KAB Survey in Key Risk Message Questions Modified Between the Two Versions

12-month Survey Question Number	24-month Survey Question Number	Question as Presented in the 24-month Survey	12-month Survey Correct Response (%)	24-month Survey % Correct Response (%)
7	8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
7a	8a	A personal history of psychiatric illness (***Correct Response Yes***)	66.6	72.0
8	9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option:		
8e	9e	Chronic non-cancer pain (***Correct Response No***)	29.8	47.0

In this 24-month survey, only one item was identified as having a low level of understanding among pharmacists (TIRF medicines are not indicated for chronic non-cancer pain; 47.0%). However, it should be noted that there was a marked improvement in the Pharmacist's correct response rate for this concept from the 12-month KAB survey to the 24-month KAB survey. It should also be noted that recognition of uses for which TIRF medicines are not indicated is not a goal of the TIRF REMS for pharmacists. Because a majority of the pharmacists surveyed demonstrated a high level of understanding of all but one item out of the 4 key risk messages the TRIG has determined that the Pharmacist Education Program is meeting the goals of the TIRF REMS.

Appendix A Pharmacy Survey Protocol

PROTOCOL TITLE:	**Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Archimedes Pharma US Inc.** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Endo Pharmaceuticals Inc.** **Galena Biopharma** **Insys Therapeutics** **Mallinckrodt** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**5.0**
DATE:	**10 Sep 2013**
APPROVED:	**FINAL**

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1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CSP	Closed System Pharmacy
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE/PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

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2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients

2. Preventing inappropriate conversion between TIRF medicines

3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI). This protocol will describe the administration of the surveys that will be conducted among pharmacists who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists around the following key information and risk messages communicated through REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of pharmacists who are enrolled in the TIRF REMS Access Program. Respondents who have participated in the first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered via the Internet through a secure website

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- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take up to 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the KAB survey results for pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions.

Qualitative research was performed with 7 pharmacists who were recruited from the list of pharmacists who completed surveys for the 12-month TIRF REMS Assessment and met the definition of "low performer", i.e., provided an incorrect response on 3 to 5 of the 7 targeted responses/questions from the 12-month TIRF REMS Assessment.

Among the pharmacists interviewed, the most notable finding was that their survey responses should be based on ("according to") the TIRF medicines label. The findings from this research have been incorporated into the survey in Appendix A. The qualitative research report can be found in Appendix C.

4.1.2 Questions and Statements on REMS Goals

The Knowledge, Attitudes, and Behaviors (KAB) questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- One question allowing for the respondent to list questions or comments.

Questionnaires will be analyzed to determine pharmacist understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

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Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

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Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors. The following question about behaviors will be asked after the key risk message questions.

Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

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4.2 Participant Recruitment

A random sample of "pharmacists in charge" from pharmacies that are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. Any pharmacist who works at an enrolled pharmacy may participate. The text of the sample written invitation to pharmacists can be found in Appendix B.

If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-respondents from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of pharmacists will be randomly selected. The unique code provided in the invitation letter will be linked to the type of pharmacy (inpatient, outpatient, or Closed System Pharmacy [CSP]) in which the pharmacist works, based on the information provided as part of the TIRF REMS Access Program enrollment.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium to thank them for their participation. The mailing will include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating pharmacists will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of pharmacies (e.g., chain and independent store) for participation.

Pharmacists will be offered Internet-based or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the Internet-based survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 pharmacists who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate

for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

Pharmacists who work at pharmacies that are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Pharmacists who have previously participated in the TIRF REMS KAB survey.
- Pharmacists or their immediate family members who have ever worked for Anesta LLC, Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; ProStrakan, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

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6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm pharmacist eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Pharmacist-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of pharmacists who do not have Internet access or prefer taking the survey over the telephone. It will also be convenient for pharmacists to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the pharmacist selects to participate in the survey via the Internet, he/she will be directed to a secured website where he/she will be instructed to complete screening questions. An Internet-based survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified time period when the Survey Coordinating Center is available.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer interviews.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question

once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to pharmacists
- The number of reminder letters issued to pharmacists
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who answered all questions presented to them
- Representativeness of pharmacists based on geography
- Description of survey participants, including:
    - Gender
    - Years of professional experience
    - How many times per month TIRF medicines dispensed in the last 6 months

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible pharmacists who completed all questions presented to them in the survey ("completers").

7.1.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

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7.1.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of completers who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if they have questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE/PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE/PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $50 honorarium, a Thank You Letter, correct survey responses to key risk message questions, and the ISI after the survey is completed. Respondent contact information is also needed in the event that a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to dispense TIRF medicines.

Appendix A Pharmacist Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

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Survey Legend

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
  West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV

Survey Legend

– Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297.

Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

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[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[ONLY TERMINATE AFTER WAVE 1]**
   - ○ No
   - ○ I don't know **[ONLY TERMINATE AFTER WAVE 1]**

3. Do you work in a pharmacy that is enrolled in the TIRF REMS Access program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Archimedes Pharma US Inc.**[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Endo Pharmaceuticals Inc. **[TERMINATE]**
   - □ Galena Biopharma **[TERMINATE]**

- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ ProStrakan, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
7a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
7d. Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

[RANDOMIZE LIST]	True	False	I don't know
11a. 8 mg oral hydromorphone/day	○	○	○
11b. 60 mg oral morphine/day	○	○	○
11c. 30 mg oral oxycodone/day	○	○	○
11d. 25 mcg transdermal fentanyl/hour	○	○	○
11e. 25 mg oral oxymorphone/day	○	○	○
11f. An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f. Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. Please answer True, False, or I don't know for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
13a.	TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
13b.	All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.	○	○	○
13c.	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

14. **[INPATIENT PHARMACIST]** Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program?

- ○ Yes
- ○ No
- ○ I don't know

15. **[OUTPATIENT PHARMACIST]** Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system?

- ○ Yes
- ○ No
- ○ I don't know

16. **[CSP OUTPATIENT PHARMACIST]** Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?

- ○ Yes
- ○ No
- ○ I don't know

17. **[INPATIENT PHARMACIST]** Please answer True, False, or I don't know for the following statement about TIRF medicines.

	True	False	I don't know
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	○	○	○

[PREAMBLE 3]

The next set of questions is about the educational materials for TIRF medicines. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

18. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q20]**
- ○ I don't know **[GO TO Q20]**

19. Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

20. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

23. What are your questions? **[MULTILINE INPUT]**

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

24. Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?

- ○ Yes
- ○ No
- ○ I don't know

25. On average, how many times per month have you dispensed TIRF medicine within the last 6 months?

- ○ None **[Go to DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

26. Please select the TIRF medicine(s) that you have dispensed within the last 6 months (select all that apply):

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda ®
- ☐ Onsolis®
- ☐ Subsys®

[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

27. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

28. In total, how many years have you been a practicing pharmacist?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

29. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $50 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey.

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Do you agree to give us your name and mailing address so we can send you the honorarium?

○ Yes

○ No **[SKIP TO CLOSING 2]**

[END CLOSING 1]

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END CLOSING 3]

[END OF SURVEY CONTENT]

Appendix B Pharmacist Invitation Letter

[CURR_DATE]

[PHARMACY_NAME]

[PHARMACY _STREET_ADDR]
[PHARMACY_CITY], [PHARMACY _STATE] [PHARMACY _ZIP]

[PHARMACY_FAX_NUMBER]

Dear [PHARMACIST_IN CHARGE]

Your Pharmacy was selected to receive this letter, because of enrollment in the TIRF REMS Access Program. We are contacting you to inform you about a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt; Mylan, Inc.; and Par Pharmaceutical, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

You are under no obligation to participate in this survey. Only one pharmacist from each enrolled pharmacy can participate. If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**. ***We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.***

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

Sincerely,

The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

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Appendix C Qualitative Research Report

FDA_1175

Appendix B Pharmacy Survey Listings and Sub-analysis Tables

Listing 1 REPORTED ADVERSE EVENTS, PRODUCT COMPLAINTS, or Requests for Medical Information

Verbatim Response
?
CAN YOU SEND A COPY OF THE FULL PRESCRIBING INFO? IS IT DIFFERENT THAN THE PACKAGE INSERT? IF NOT, THEN DON'T NEED IT, I CAN LOOK AT THE PACKAGE INSERT
dose conversions form other narcotics
DOSING RELATED
equivalent does,evaluation of pt on very high and multiple pain rx's by md
I have no questions
I just need to go back and read the section about what other opioid doses need to be met before starting this med.
I questioned the requirements for opioid use and dose suggestions. They have since been clarified.
I would like to have a visit from a rep.
If insurance has lapsed, is there a problem with selling a product out-of-pocket?
Making sure the proper dose is used and titrated for the patient based on history
n/a
na
Need alot more specific prescribing info on these meds
need complete guidelines about the products falls under TIRF
NONE
what is considered opioid tolerant patient?
Why do you educate that these medications are only for cancer pain yet they are allowed to be prescribed for non-cancer pain

LISTING 2. VERBATIM RESPONSES TO QUESTION 22 (QUESTIONS ABOUT THE INFORMATION IN THE FULL PRESCRIBING INFORMATION OR MEDICATION GUIDE)

Verbatim Response
?
CAN YOU SEND A COPY OF THE FULL PRESCRIBING INFO? IS IT DIFFERENT THAN THE PACKAGE INSERT? IF NOT, THEN DON'T NEED IT, I CAN LOOK AT THE PACKAGE INSERT
dose conversions form other narcotics
DOSING RELATED
equivalent does,evaluation of pt on very high and multiple pain rx's by md
I have no questions
I just need to go back and read the section about what other opioid doses need to be met before starting this med.
I questioned the requirements for opioid use and dose suggestions. They have since been clarified.
I would like to have a visit from a rep.
If insurance has lapsed, is there a problem with selling a product out-of-pocket?
Making sure the proper dose is used and titrated for the patient based on history
n/a
na
Need alot more specific prescribing info on these meds
need complete guidelines about the products falls under TIRF
NONE
what is considered opioid tolerant patient?
Why do you educate that these medications are only for cancer pain yet they are allowed to be prescribed for non-cancer pain

TABLE 1.1 SURVEY ADMINISTRATION STATISTICS

Question	N	%
The number of invitations issued to pharmacists	7167	
The number of reminder letters issued to pharmacists	13,215	
The number of respondents screened for participation	372[1]	
The number of respondents eligible for participation	300	
The number of respondents eligible for participation who answered all questions presented to them	300	80.6
By Telephone	9	2.4
By Internet	291	78.2

[1] This is the denominator for the percentages in this table (N=372).

TABLE 1.2 TIME TO COMPLETE SURVEY (COMPLETERS ONLY)

Time to Complete Survey			
Summary Statistic	**Telephone**	**Internet**	**Total**
N	9	291	300
Mean (SD)	18.0 (1.81)	14.3 (8.75)	14.4 (8.64)
Minimum	15	4	4
Median	18.0	11.6	11.8
Maximum	20	85	85
Category	**Telephone**	**Internet**	**Total**
0 to <5 Minutes	0	1	1
5 to <10 Minutes	0	90	90
10 to <15 Minutes	0	106	106
15 to <20 Minutes	8	47	55
20 to <25 Minutes	1	21	22
25 to <30 Minutes	0	12	12
30 Minutes or More	0	14	14

TABLE 1.3 SURVEY PARTICIPANT SCREENING RESULTS

Question	All Respondents N=372		Eligible and Complete Respondents N=300	
	N	%	N	%
Question 1: Do you agree to participate in this survey?				
Yes	371	99.7	300	100.0
No[1]	1	0.3	0	0.0
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.				
Yes [1]	8	2.2		
No	339	91.1	300	100.0
I don't know [1]	24	6.5		
Question not asked [2]	1	0.3		
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access program?				
Yes	304	81.7	300	100.0
No[1]	8	2.2		
I don't know[1]	27	7.3		
Question not asked [2]	33	8.9		
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply. [3]				
Anesta LLC[1]	0	0.0		
Archimedes Pharma US Inc.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	0	0.0		

Question	All Respondents N=372		Eligible and Complete Respondents N=300	
	N	%	N	%
Endo Pharmaceuticals Inc. [1]	1	0.3		
Galena Biopharma[1]	0	0.0		
Insys Therapeutics[1]	0	0.0		
Mallinckrodt[1]	0	0.0		
McKesson Specialty Care Solutions[1]	0	0.0		
Meda Pharmaceuticals[1]	0	0.0		
Mylan, Inc.[1]	0	0.0		
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
RelayHealth[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	0	0.0		
United BioSource Corporation[1]	0	0.0		
FDA[1]	1	0.3		
None of these apply[4]	300	80.6	300	100.0
I don't know[1]	0	0.0		
Prefer not to answer[1]	2	0.5		
Question not asked [2]	68	18.3		

[1] Ineligible to participate in the survey.

[2] Question not asked due to a previous question elimination.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Ineligible if selected in addition to another item.

TABLE 2 DESCRIPTION OF ELIGIBLE AND COMPLETE RESPONDENTS

Question	Pharmacists N=300	
	N	%
Question 24: Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?		
Yes	242	80.7
No	52	17.3
I don't know	6	2.0
Question 25: On average, how many times per month have you dispensed TIRF medicine within the last 6 months?		
None	145	48.3
1 – 2 times per month	90	30.0
3 – 5 times per month	32	10.7
More than 5 times per month	15	5.0
I don't remember	18	6.0
Question 26: Please select the TIRF medicine(s) that you have dispensed within the last 6 months (select all that apply):		
Abstral®	8	5.2
Actiq® or generic Actiq®	120	77.4
Fentora®	57	36.8
Lazanda®	6	3.9
Onsolis®	1	0.6
Subsys®	17	11.0
N/A (answered ***None*** to Question 25)	145	
Question 27: What is your gender?		
Male	183	61.0
Female	111	37.0
Prefer not to answer	6	2.0

Question	Pharmacists N=300	
	N	%
Question 28: In total, how many years have you been a practicing pharmacist?		
Less than 3 years	23	7.7
3 - 5 years	41	13.7
6 - 10 years	40	13.3
11 - 15 years	34	11.3
More than 15 years	157	52.3
Prefer not to answer	5	1.7

TABLE 2.1 GEOGRAPHIC DISTRIBUTION (BASED ON QUESTION 29 – IN WHICH STATE OR US TERRITORY DO YOU PRACTICE)

Geographic Region [1]	Eligible and Complete Respondents N=300		Enrolled in TIRF REMS Access Program on 10Oct2013 N=38597	
	N	%	N	%
Northeast	78	26.0	7834	20.3
Midwest	72	24.0	8027	20.8
South	97	32.3	15027	38.9
West	52	17.3	7549	19.6
Other	0	0.0	160	0.4
Prefer not to answer	1	0.3	0	0.0

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

TABLE 3 RESPONSES TO ALL QUESTIONS ABOUT THE SAFE USE OF TIRF MEDICINES

Question	Pharmacists N=300	
	N	%
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer		
True [1]	271	90.3
False	23	7.7
I don't know	6	2.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
False [1]	242	80.7
True	41	13.7
I don't know	17	5.7
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
False [1]	228	76.0
True	52	17.3
I don't know	20	6.7
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.		
False [1]	196	65.3
True	80	26.7
I don't know	24	8.0

Question	Pharmacists N=300	
	N	%
6b: A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
False [1]	224	74.7
True	50	16.7
I don't know	26	8.7
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [1]	258	86.0
False	27	9.0
I don't know	15	5.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [1]	281	93.7
False	2	0.7
I don't know	17	5.7
7c: TIRF medicines may be used in opioid non-tolerant patients.		
False [1]	246	82.0
True	40	13.3
I don't know	14	4.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True [1]	248	82.7
False	38	12.7
I don't know	14	4.7

Question	Pharmacists N=300	
	N	%
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [1]	290	96.7
False	5	1.7
I don't know	5	1.7
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes [1]	216	72.0
No	48	16.0
I don't know	36	12.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [1]	297	99.0
No	0	0.0
I don't know	3	1.0
8c: A family history of asthma		
No [1]	245	81.7
Yes	38	12.7
I don't know	17	5.7
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
No [1]	254	84.7
Yes	31	10.3
I don't know	15	5.0

Question	Pharmacists N=300	
	N	%
9b: Headache or migraine pain		
No [1]	277	92.3
Yes	8	2.7
I don't know	15	5.0
9c: Dental pain		
No [1]	290	96.7
Yes	3	1.0
I don't know	7	2.3
9d: Breakthrough pain from cancer		
Yes [1]	268	89.3
No	27	9.0
I don't know	5	1.7
9e: Chronic non-cancer pain		
No [1]	141	47.0
Yes	126	42.0
I don't know	33	11.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True [1]	282	94.0
False	10	3.3
I don't know	8	2.7
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
False [1]	284	94.7
True	6	2.0
I don't know	10	3.3

Question	Pharmacists N=300	
	N	%
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True [1]	276	92.0
False	5	1.7
I don't know	19	6.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True [1]	274	91.3
False	10	3.3
I don't know	16	5.3
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True [1]	237	79.0
False	29	9.7
I don't know	34	11.3
11b: 60 mg oral morphine/day		
True [1]	255	85.0
False	14	4.7
I don't know	31	10.3
11c: 30 mg oral oxycodone/day		
True [1]	214	71.3
False	44	14.7
I don't know	42	14.0
11d: 25 mcg transdermal fentanyl/hour		
True [1]	216	72.0
False	45	15.0
I don't know	39	13.0

Question	Pharmacists N=300	
	N	%
11e: 25 mg oral oxymorphone/day		
True [1]	213	71.0
False	29	9.7
I don't know	58	19.3
11f: An equianalgesic dose of another oral opioid		
True [1]	177	59.0
False	61	20.3
I don't know	62	20.7
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.		
13a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.		
False [1]	274	91.3
True	8	2.7
I don't know	18	6.0
13b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.		
True [1]	282	94.0
False	6	2.0
I don't know	12	4.0
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.		
False [1]	289	96.3
True	6	2.0
I don't know	5	1.7

Question	Pharmacists N=300	
	N	%
Question 17: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient pharmacists, only)		
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.		
False [1]	13	86.7
True	0	0.0
I don't know	2	13.3

[1] Correct response

TABLE 4 RESPONSES TO QUESTIONS ABOUT THE EDUCATIONAL MATERIALS

Question	Pharmacists N=300	
	N	%
Question 18: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?		
Yes	291	97.0
No	1	0.3
I don't know	8	2.7
Question 19: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?[1]		
Yes	223	76.6
No	61	21.0
I don't know	7	2.4
N/A (answered ***No*** or ***I don't know*** to Question 18)	9	
Question 20: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?		
Yes	297	99.0
No	1	0.3
I don't know	2	0.7
Question 21: Did you read the Medication Guide for the TIRF medicine that you dispense? [1]		
Yes	250	84.2
No	39	13.1
I don't know	8	2.7
N/A (answered ***No*** or ***I don't know*** to Question 20)	3	
Question 22: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide? [2]		
Yes[2]	21	7.0
No	259	86.3
I don't know	20	6.7

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

[2] Verbatim texts for questions about the information in the Full Prescribing Information are presented in Listing 2.

TABLE 5 RESPONSES TO QUESTIONS ABOUT ACTIVITIES WHEN DISPENSING TIRF MEDICINES

Question	Pharmacists N=300	
	N	%
Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.		
12a: Ask patients (or their caregivers) about the presence of children in the home		
Always	167	55.7
Only with the first prescription	54	18.0
Sometimes	54	18.0
Never	13	4.3
I don't know	12	4.0
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else		
Always	208	69.3
Only with the first prescription	52	17.3
Sometimes	26	8.7
Never	8	2.7
I don't know	6	2.0
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal		
Always	198	66.0
Only with the first prescription	57	19.0
Sometimes	29	9.7
Never	8	2.7
I don't know	8	2.7

Question	Pharmacists N=300	
	N	%
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure		
Always	223	74.3
Only with the first prescription	44	14.7
Sometimes	23	7.7
Never	5	1.7
I don't know	5	1.7
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines		
Always	198	66.0
Only with the first prescription	67	22.3
Sometimes	26	8.7
Never	4	1.3
I don't know	5	1.7
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine		
Always	274	91.3
Only with the first prescription	11	3.7
Sometimes	10	3.3
Never	0	0.0
I don't know	5	1.7
Question 14: Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program? [Inpatient pharmacists, only] [1]		
Yes	8	53.3
No	4	26.7
I don't know	3	20.0

Question	Pharmacists N=300	
	N	%
Question 15: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? [Outpatient pharmacists, only] [1]		
Yes	231	82.2
No	5	1.8
I don't know	45	16.0
Question 16: Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center? [CSP Outpatient pharmacists, only] [1]		
Yes	2	50.0
No	0	0.0
I don't know	2	50.0

[1] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of pharmacists to whom this question was presented.

TABLE 6.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer		
True [1]	271	90.3 (86.4, 93.4)
False	23	7.7
I don't know	6	2.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
False [1]	242	80.7 (75.7, 85.0)
True	41	13.7
I don't know	17	5.7
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
False [1]	228	76.0 (70.8, 80.7)
True	52	17.3
I don't know	20	6.7

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [1]	258	86.0 (81.6, 89.7)
False	27	9.0
I don't know	15	5.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [1]	281	93.7 (90.3, 96.1)
False	2	0.7
I don't know	17	5.7
7c: TIRF medicines may be used in opioid non-tolerant patients.		
False [1]	246	82.0 (77.2, 86.2)
True	40	13.3
I don't know	14	4.7

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True [1]	248	82.7 (77.9, 86.8)
False	38	12.7
I don't know	14	4.7

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer				
True [1]	241	92.0 (88.0, 95.0)	30	78.9 (62.7, 90.4)
False	16	6.1	7	18.4
I don't know	5	1.9	1	2.6
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	211	80.5 (75.2, 85.1)	31	81.6 (65.7, 92.3)
True	37	14.1	4	10.5
I don't know	14	5.3	3	7.9

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	202	77.1 (71.5, 82.0)	26	68.4 (51.3, 82.5)
True	44	16.8	8	21.1
I don't know	16	6.1	4	10.5
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	223	85.1 (80.2, 89.2)	35	92.1 (78.6, 98.3)
False	25	9.5	2	5.3
I don't know	14	5.3	1	2.6
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	248	94.7 (91.2, 97.0)	33	86.8 (71.9, 95.6)
False	1	0.4	1	2.6
I don't know	13	5.0	4	10.5
7c: TIRF medicines may be used in opioid non-tolerant patients.				
False [1]	214	81.7 (76.5, 86.2)	32	84.2 (68.7, 94.0)
True	36	13.7	4	10.5
I don't know	12	4.6	2	5.3

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	219	83.6 (78.5, 87.9)	29	76.3 (59.8, 88.6)
False	30	11.5	8	21.1
I don't know	13	5.0	1	2.6

[1] Correct response

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:						
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer						
True [1]	85	93.4 (86.2, 97.5)	137	89.5 (83.6, 93.9)	42	89.4 (76.9, 96.5)
False	4	4.4	14	9.2	5	10.6
I don't know	2	2.2	2	1.3	0	0.0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before						
False [1]	69	75.8 (65.7, 84.2)	127	83.0 (76.1, 88.6)	40	85.1 (71.7, 93.8)
True	16	17.6	19	12.4	4	8.5
I don't know	6	6.6	7	4.6	3	6.4
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy						
False [1]	63	69.2 (58.7, 78.5)	123	80.4 (73.2, 86.4)	36	76.6 (62.0, 87.7)
True	19	20.9	22	14.4	10	21.3
I don't know	9	9.9	8	5.2	1	2.1

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
True [1]	75	82.4 (73.0, 89.6)	132	86.3 (79.8, 91.3)	43	91.5 (79.6, 97.6)
False	10	11.0	13	8.5	4	8.5
I don't know	6	6.6	8	5.2	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
True [1]	85	93.4 (86.2, 97.5)	144	94.1 (89.1, 97.3)	43	91.5 (79.6, 97.6)
False	1	1.1	0	0.0	1	2.1
I don't know	5	5.5	9	5.9	3	6.4
7c: TIRF medicines may be used in opioid non-tolerant patients.						
False [1]	71	78.0 (68.1, 86.0)	125	81.7 (74.6, 87.5)	43	91.5 (79.6, 97.6)
True	16	17.6	20	13.1	3	6.4
I don't know	4	4.4	8	5.2	1	2.1
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.						
True [1]	75	82.4 (73.0, 89.6)	125	81.7 (74.6, 87.5)	41	87.2 (74.3, 95.2)
False	13	14.3	17	11.1	6	12.8
I don't know	3	3.3	11	7.2	0	0.0

[1] Correct response

TABLE 6.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer				
True [1]	264	90.7 (86.8, 93.8)	7	77.8 (40.0, 97.2)
False	23	7.9	0	0.0
I don't know	4	1.4	2	22.2
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	236	81.1 (76.1, 85.4)	6	66.7 (29.9, 92.5)
True	39	13.4	2	22.2
I don't know	16	5.5	1	11.1
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	222	76.3 (71.0, 81.1)	6	66.7 (29.9, 92.5)
True	51	17.5	1	11.1
I don't know	18	6.2	2	22.2

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	250	85.9 (81.4, 89.7)	8	88.9 (51.8, 99.7)
False	27	9.3	0	0.0
I don't know	14	4.8	1	11.1
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	272	93.5 (90.0, 96.0)	9	100.0 (66.4, 100.0)
False	2	0.7	0	0.0
I don't know	17	5.8	0	0.0
7c: TIRF medicines may be used in opioid non-tolerant patients.				
False [1]	239	82.1 (77.2, 86.4)	7	77.8 (40.0, 97.2)
True	39	13.4	1	11.1
I don't know	13	4.5	1	11.1
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	241	82.8 (78.0, 87.0)	7	77.8 (40.0, 97.2)
False	36	12.4	2	22.2
I don't know	14	4.8	0	0.0

[1] Correct response

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer								
True [1]	23	100.0 (85.2,100.0)	38	92.7 (80.1, 98.5)	65	87.8 (78.2, 94.3)	142	90.4 (84.7, 94.6)
False	0	0.0	3	7.3	5	6.8	14	8.9
I don't know	0	0.0	0	0.0	4	5.4	1	0.6
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	20	87.0 (66.4, 97.2)	36	87.8 (73.8, 95.9)	56	75.7 (64.3, 84.9)	127	80.9 (73.9, 86.7)
True	2	8.7	4	9.8	11	14.9	23	14.6
I don't know	1	4.3	1	2.4	7	9.5	7	4.5

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	21	91.3 (72.0, 98.9)	38	92.7 (80.1, 98.5)	52	70.3 (58.5, 80.3)	113	72.0 (64.3, 78.8)
True	2	8.7	3	7.3	12	16.2	35	22.3
I don't know	0	0.0	0	0.0	10	13.5	9	5.7
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	23	100.0 (85.2,100.0)	39	95.1 (83.5, 99.4)	63	85.1 (75.0, 92.3)	129	82.2 (75.3, 87.8)
False	0	0.0	2	4.9	6	8.1	19	12.1
I don't know	0	0.0	0	0.0	5	6.8	9	5.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	21	91.3 (72.0, 98.9)	39	95.1 (83.5, 99.4)	71	95.9 (88.6, 99.2)	147	93.6 (88.6, 96.9)
False	1	4.3	0	0.0	0	0.0	1	0.6
I don't know	1	4.3	2	4.9	3	4.1	9	5.7

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	23	100.0 (85.2,100.0)	40	97.6 (87.1, 99.9)	62	83.8 (73.4, 91.3)	118	75.2 (67.6, 81.7)
True	0	0.0	0	0.0	5	6.8	34	21.7
I don't know	0	0.0	1	2.4	7	9.5	5	3.2
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	20	87.0 (66.4, 97.2)	32	78.0 (62.4, 89.4)	59	79.7 (68.8, 88.2)	133	84.7 (78.1, 90.0)
False	1	4.3	7	17.1	10	13.5	20	12.7
I don't know	2	8.7	2	4.9	5	6.8	4	2.5

[1] Correct response

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer								
True [1]	131	90.3 (84.3, 94.6)	82	91.1 (83.2, 96.1)	26	81.3 (63.6, 92.8)	15	100.0 (78.2, 100.0)
False	11	7.6	7	7.8	5	15.6	0	0.0
I don't know	3	2.1	1	1.1	1	3.1	0	0.0

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	121	83.4 (76.4, 89.1)	70	77.8 (67.8, 85.9)	28	87.5 (71.0, 96.5)	9	60.0 (32.3, 83.7)
True	17	11.7	15	16.7	3	9.4	4	26.7
I don't know	7	4.8	5	5.6	1	3.1	2	13.3
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	116	80.0 (72.6, 86.2)	64	71.1 (60.6, 80.2)	25	78.1 (60.0, 90.7)	9	60.0 (32.3, 83.7)
True	21	14.5	19	21.1	5	15.6	4	26.7
I don't know	8	5.5	7	7.8	2	6.3	2	13.3
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	129	89.0 (82.7, 93.6)	76	84.4 (75.3, 91.2)	27	84.4 (67.2, 94.7)	10	66.7 (38.4, 88.2)
False	10	6.9	11	12.2	3	9.4	3	20.0
I don't know	6	4.1	3	3.3	2	6.3	2	13.3

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	135	93.1 (87.7, 96.6)	87	96.7 (90.6, 99.3)	29	90.6 (75.0, 98.0)	14	93.3 (68.1, 99.8)
False	0	0.0	0	0.0	1	3.1	0	0.0
I don't know	10	6.9	3	3.3	2	6.3	1	6.7
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	130	89.7 (83.5, 94.1)	71	78.9 (69.0, 86.8)	23	71.9 (53.3, 86.3)	8	53.3 (26.6, 78.7)
True	10	6.9	18	20.0	7	21.9	4	26.7
I don't know	5	3.4	1	1.1	2	6.3	3	20.0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	121	83.4 (76.4, 89.1)	78	86.7 (77.9, 92.9)	26	81.3 (63.6, 92.8)	10	66.7 (38.4, 88.2)
False	19	13.1	9	10.0	3	9.4	4	26.7
I don't know	5	3.4	3	3.3	3	9.4	1	6.7

[1] Correct response

TABLE 6.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

Demonstrated Understanding	Eligible and Complete Respondents N=300	
	N	%
0 correct responses	2	0.7
1 correct response	2	0.7
2 correct responses	6	2.0
3 correct responses	7	2.3
4 correct responses	22	7.3
5 correct responses	45	15.0
6 correct responses	86	28.7
7 correct responses	130	43.3
Average number of correct responses	5.9	(5.7, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	%	N	%
0 correct responses	2	0.8	0	0.0
1 correct response	2	0.8	0	0.0
2 correct responses	5	1.9	1	2.6
3 correct responses	5	1.9	2	5.3
4 correct responses	17	6.5	5	13.2
5 correct responses	38	14.5	7	18.4
6 correct responses	78	29.8	8	21.1
7 correct responses	115	43.9	15	39.5
Average number of correct responses	5.9	(5.7, 7.0) [1]	5.7	(5.0, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	2	1.3	0	0.0
1 correct response	2	2.2	0	0.0	0	0.0
2 correct responses	4	4.4	1	0.7	0	0.0
3 correct responses	2	2.2	4	2.6	1	2.1
4 correct responses	7	7.7	12	7.8	2	4.3
5 correct responses	17	18.7	21	13.7	6	12.8
6 correct responses	19	20.9	45	29.4	19	40.4
7 correct responses	40	44.0	68	44.4	19	40.4
Average number of correct responses	5.7	(5.3, 7.0) [1]	6.0	(5.6, 7.0) [1]	6.1	(5.5, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=291		S-4b Telephone N=9	
	N	%	N	%
0 correct responses	2	0.7	0	0.0
1 correct response	2	0.7	0	0.0
2 correct responses	5	1.7	1	11.1
3 correct responses	7	2.4	0	0.0
4 correct responses	21	7.2	1	11.1
5 correct responses	44	15.1	1	11.1
6 correct responses	83	28.5	3	33.3
7 correct responses	127	43.6	3	33.3
Average number of correct responses	5.9	(5.7, 7.0) [1]	5.6	(4.3, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	1.4	0	0.0
1 correct response	0	0.0	0	0.0	1	1.4	1	0.6
2 correct responses	0	0.0	0	0.0	4	5.4	2	1.3
3 correct responses	0	0.0	0	0.0	1	1.4	6	3.8
4 correct responses	0	0.0	0	0.0	6	8.1	16	10.2
5 correct responses	2	8.7	4	9.8	5	6.8	33	21.0
6 correct responses	6	26.1	17	41.5	25	33.8	36	22.9
7 correct responses	15	65.2	20	48.8	31	41.9	63	40.1
Average number of correct responses	6.6	(5.7, 7.0) [1]	6.4	(5.7, 7.0) [1]	5.8	(5.3, 7.0) [1]	5.8	(5.5, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 6.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	3.1	0	0.0
1 correct response	1	0.7	0	0.0	0	0.0	1	6.7
2 correct responses	1	0.7	2	2.2	2	6.3	1	6.7
3 correct responses	3	2.1	3	3.3	0	0.0	1	6.7
4 correct responses	10	6.9	7	7.8	2	6.3	1	6.7
5 correct responses	19	13.1	17	18.9	4	12.5	4	26.7
6 correct responses	41	28.3	25	27.8	9	28.1	4	26.7
7 correct responses	70	48.3	36	40.0	14	43.8	3	20.0
Average number of correct responses	6.1	(5.8, 7.0) [1]	5.9	(5.4, 7.0) [1]	5.8	(5.1, 7.0) [1]	5.0	(4.1, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
No [1]	254	84.7 (80.1, 88.6)
Yes	31	10.3
I don't know	15	5.0
9b: Headache or migraine pain		
No [1]	277	92.3 (88.7, 95.1)
Yes	8	2.7
I don't know	15	5.0
9c: Dental pain		
No [1]	290	96.7 (94.0, 98.4)
Yes	3	1.0
I don't know	7	2.3

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
9d: Breakthrough pain from cancer		
Yes [1]	268	89.3 (85.3, 92.6)
No	27	9.0
I don't know	5	1.7
9e: Chronic non-cancer pain		
No [1]	141	47.0 (41.2, 52.8)
Yes	126	42.0
I don't know	33	11.0

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
No [1]	221	84.4 (79.4, 88.5)	33	86.8 (71.9, 95.6)
Yes	27	10.3	4	10.5
I don't know	14	5.3	1	2.6
9b: Headache or migraine pain				
No [1]	245	93.5 (89.8, 96.2)	32	84.2 (68.7, 94.0)
Yes	6	2.3	2	5.3
I don't know	11	4.2	4	10.5

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
9c: Dental pain				
No [1]	254	96.9 (94.1, 98.7)	36	94.7 (82.3, 99.4)
Yes	3	1.1	0	0.0
I don't know	5	1.9	2	5.3
9d: Breakthrough pain from cancer				
Yes [1]	233	88.9 (84.5, 92.5)	35	92.1 (78.6, 98.3)
No	25	9.5	2	5.3
I don't know	4	1.5	1	2.6
9e: Chronic non-cancer pain				
No [1]	129	49.2 (43.0, 55.5)	12	31.6 (17.5, 48.7)
Yes	106	40.5	20	52.6
I don't know	27	10.3	6	15.8

[1] Correct response

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.						
9a: Acute or postoperative pain						
No [1]	69	75.8 (65.7, 84.2)	136	88.9 (82.8, 93.4)	42	89.4 (76.9, 96.5)
Yes	16	17.6	9	5.9	5	10.6
I don't know	6	6.6	8	5.2	0	0.0
9b: Headache or migraine pain						
No [1]	83	91.2 (83.4, 96.1)	139	90.8 (85.1, 94.9)	46	97.9 (88.7, 99.9)
Yes	2	2.2	6	3.9	0	0.0
I don't know	6	6.6	8	5.2	1	2.1

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9c: Dental pain						
No [1]	86	94.5 (87.6, 98.2)	148	96.7 (92.5, 98.9)	47	100.0 (92.5, 100.0)
Yes	3	3.3	0	0.0	0	0.0
I don't know	2	2.2	5	3.3	0	0.0
9d: Breakthrough pain from cancer						
Yes [1]	79	86.8 (78.1, 93.0)	136	88.9 (82.8, 93.4)	45	95.7 (85.5, 99.5)
No	10	11.0	14	9.2	2	4.3
I don't know	2	2.2	3	2.0	0	0.0
9e: Chronic non-cancer pain						
No [1]	38	41.8 (31.5, 52.6)	77	50.3 (42.1, 58.5)	23	48.9 (34.1, 63.9)
Yes	42	46.2	58	37.9	22	46.8
I don't know	11	12.1	18	11.8	2	4.3

[1] Correct response

TABLE 7.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
No [1]	247	84.9 (80.2, 88.8)	7	77.8 (40.0, 97.2)
Yes	30	10.3	1	11.1
I don't know	14	4.8	1	11.1
9b: Headache or migraine pain				
No [1]	268	92.1 (88.4, 94.9)	9	100.0 (66.4, 100.0)
Yes	8	2.7	0	0.0
I don't know	15	5.2	0	0.0
9c: Dental pain				
No [1]	281	96.6 (93.8, 98.3)	9	100.0 (66.4, 100.0)
Yes	3	1.0	0	0.0
I don't know	7	2.4	0	0.0

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
9d: Breakthrough pain from cancer				
Yes [1]	260	89.3 (85.2, 92.6)	8	88.9 (51.8, 99.7)
No	26	8.9	1	11.1
I don't know	5	1.7	0	0.0
9e: Chronic non-cancer pain				
No [1]	138	47.4 (41.6, 53.3)	3	33.3 (7.5, 70.1)
Yes	122	41.9	4	44.4
I don't know	31	10.7	2	22.2

[1] Correct response

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	18	78.3 (56.3, 92.5)	38	92.7 (80.1, 98.5)	62	83.8 (73.4, 91.3)	132	84.1 (77.4, 89.4)
Yes	2	8.7	2	4.9	9	12.2	18	11.5
I don't know	3	13.0	1	2.4	3	4.1	7	4.5

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	22	95.7 (78.1, 99.9)	39	95.1 (83.5, 99.4)	66	89.2 (79.8, 95.2)	146	93.0 (87.8, 96.5)
Yes	0	0.0	0	0.0	3	4.1	5	3.2
I don't know	1	4.3	2	4.9	5	6.8	6	3.8
9c: Dental pain								
No [1]	23	100.0 (85.2,100.0)	41	100.0 (91.4,100.0)	71	95.9 (88.6, 99.2)	151	96.2 (91.9, 98.6)
Yes	0	0.0	0	0.0	1	1.4	2	1.3
I don't know	0	0.0	0	0.0	2	2.7	4	2.5
9d: Breakthrough pain from cancer								
Yes [1]	22	95.7 (78.1, 99.9)	38	92.7 (80.1, 98.5)	68	91.9 (83.2, 97.0)	137	87.3 (81.0, 92.0)
No	1	4.3	3	7.3	4	5.4	18	11.5
I don't know	0	0.0	0	0.0	2	2.7	2	1.3

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	12	52.2 (30.6, 73.2)	20	48.8 (32.9, 64.9)	32	43.2 (31.8, 55.3)	74	47.1 (39.1, 55.2)
Yes	7	30.4	19	46.3	31	41.9	68	43.3
I don't know	4	17.4	2	4.9	11	14.9	15	9.6

[1] Correct response

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.								
9a: Acute or postoperative pain								
No [1]	125	86.2 (79.5, 91.4)	78	86.7 (77.9, 92.9)	26	81.3 (63.6, 92.8)	10	66.7 (38.4, 88.2)
Yes	11	7.6	11	12.2	4	12.5	4	26.7
I don't know	9	6.2	1	1.1	2	6.3	1	6.7

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	131	90.3 (84.3, 94.6)	88	97.8 (92.2, 99.7)	29	90.6 (75.0, 98.0)	12	80.0 (51.9, 95.7)
Yes	4	2.8	1	1.1	1	3.1	2	13.3
I don't know	10	6.9	1	1.1	2	6.3	1	6.7
9c: Dental pain								
No [1]	143	98.6 (95.1, 99.8)	88	97.8 (92.2, 99.7)	29	90.6 (75.0, 98.0)	13	86.7 (59.5, 98.3)
Yes	0	0.0	1	1.1	1	3.1	1	6.7
I don't know	2	1.4	1	1.1	2	6.3	1	6.7
9d: Breakthrough pain from cancer								
Yes [1]	135	93.1 (87.7, 96.6)	82	91.1 (83.2, 96.1)	25	78.1 (60.0, 90.7)	11	73.3 (44.9, 92.2)
No	10	6.9	7	7.8	4	12.5	4	26.7
I don't know	0	0.0	1	1.1	3	9.4	0	0.0

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	78	53.8 (45.3, 62.1)	43	47.8 (37.1, 58.6)	9	28.1 (13.7, 46.7)	5	33.3 (11.8, 61.6)
Yes	49	33.8	38	42.2	20	62.5	9	60.0
I don't know	18	12.4	9	10.0	3	9.4	1	6.7

[1] Correct response

TABLE 7.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

Demonstrated Understanding	Eligible and Complete Respondents N=300	
	N	%
0 correct responses	2	0.7
1 correct response	4	1.3
2 correct responses	12	4.0
3 correct responses	47	15.7
4 correct responses	114	38.0
5 correct responses	121	40.3
Average number of correct responses	4.1	(3.9, 5.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	%	N	%
0 correct responses	2	0.8	0	0.0
1 correct response	2	0.8	2	5.3
2 correct responses	12	4.6	0	0.0
3 correct responses	38	14.5	9	23.7
4 correct responses	98	37.4	16	42.1
5 correct responses	110	42.0	11	28.9
Average number of correct responses	4.1	(3.9, 5.0) [1]	3.9	(3.4, 5.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	2	1.3	0	0.0
1 correct response	2	2.2	2	1.3	0	0.0
2 correct responses	7	7.7	4	2.6	1	2.1
3 correct responses	18	19.8	20	13.1	6	12.8
4 correct responses	35	38.5	59	38.6	17	36.2
5 correct responses	29	31.9	66	43.1	23	48.9
Average number of correct responses	3.9	(3.6, 5.0) [1]	4.2	(3.9, 5.0) [1]	4.3	(3.8, 5.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=291		S-4b Telephone N=9	
	N	%	N	%
0 correct responses	2	0.7	0	0.0
1 correct response	4	1.4	0	0.0
2 correct responses	12	4.1	0	0.0
3 correct responses	44	15.1	3	33.3
4 correct responses	111	38.1	3	33.3
5 correct responses	118	40.5	3	33.3
Average number of correct responses	4.1	(3.9, 5.0) [1]	4.0	(2.9, 5.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	1.4	0	0.0
1 correct response	0	0.0	0	0.0	1	1.4	3	1.9
2 correct responses	1	4.3	1	2.4	2	2.7	8	5.1
3 correct responses	3	13.0	3	7.3	14	18.9	26	16.6
4 correct responses	9	39.1	20	48.8	28	37.8	57	36.3
5 correct responses	10	43.5	17	41.5	28	37.8	63	40.1
Average number of correct responses	4.2	(3.5, 5.0) [1]	4.3	(3.8, 5.0) [1]	4.0	(3.7, 5.0) [1]	4.1	(3.8, 5.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	3.1	0	0.0
1 correct response	2	1.4	0	0.0	0	0.0	2	13.3
2 correct responses	5	3.4	3	3.3	3	9.4	1	6.7
3 correct responses	23	15.9	8	8.9	9	28.1	4	26.7
4 correct responses	44	30.3	46	51.1	10	31.3	5	33.3
5 correct responses	71	49.0	33	36.7	9	28.1	3	20.0
Average number of correct responses	4.2	(3.9, 5.0) [1]	4.2	(3.9, 5.0) [1]	3.7	(3.1, 5.0) [1]	3.4	(2.6, 5.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

Client: TRIG Project: TIRF Wave 2

Report Run Date and Time: 10/31/2013 11:28:00 AM

TABLE 8.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [1]	290	96.7 (94.0, 98.4)
False	5	1.7
I don't know	5	1.7
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes [1]	216	72.0 (66.6, 77.0)
No	48	16.0
I don't know	36	12.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [1]	297	99.0 (97.1, 99.8)
No	0	0.0
I don't know	3	1.0

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True [1]	282	94.0 (90.7, 96.4)
False	10	3.3
I don't know	8	2.7

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	253	96.6 (93.6, 98.4)	37	97.4 (86.2, 99.9)
False	4	1.5	1	2.6
I don't know	5	1.9	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	192	73.3 (67.5, 78.5)	24	63.2 (46.0, 78.2)
No	39	14.9	9	23.7
I don't know	31	11.8	5	13.2

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	259	98.9 (96.7, 99.8)	38	100.0 (90.7, 100.0)
No	0	0.0	0	0.0
I don't know	3	1.1	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	248	94.7 (91.2, 97.0)	34	89.5 (75.2, 97.1)
False	7	2.7	3	7.9
I don't know	7	2.7	1	2.6

[1] Correct response

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
True [1]	87	95.6 (89.1, 98.8)	148	96.7 (92.5, 98.9)	46	97.9 (88.7, 99.9)
False	2	2.2	2	1.3	1	2.1
I don't know	2	2.2	3	2.0	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.						
8a: A personal history of psychiatric illness						
Yes [1]	70	76.9 (66.9, 85.1)	107	69.9 (62.0, 77.1)	33	70.2 (55.1, 82.7)
No	12	13.2	24	15.7	10	21.3
I don't know	9	9.9	22	14.4	4	8.5

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse						
Yes [1]	89	97.8 (92.3, 99.7)	152	99.3 (96.4, 100.0)	47	100.0 (92.5, 100.0)
No	0	0.0	0	0.0	0	0.0
I don't know	2	2.2	1	0.7	0	0.0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
True [1]	85	93.4 (86.2, 97.5)	143	93.5 (88.3, 96.8)	45	95.7 (85.5, 99.5)
False	3	3.3	6	3.9	1	2.1
I don't know	3	3.3	4	2.6	1	2.1

[1] Correct response

TABLE 8.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	281	96.6 (93.8, 98.3)	9	100.0 (66.4, 100.0)
False	5	1.7	0	0.0
I don't know	5	1.7	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	210	72.2 (66.6, 77.2)	6	66.7 (29.9, 92.5)
No	46	15.8	2	22.2
I don't know	35	12.0	1	11.1
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	288	99.0 (97.0, 99.8)	9	100.0 (66.4, 100.0)
No	0	0.0	0	0.0
I don't know	3	1.0	0	0.0

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	273	93.8 (90.4, 96.3)	9	100.0 (66.4, 100.0)
False	10	3.4	0	0.0
I don't know	8	2.7	0	0.0

[1] Correct response

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	23	100.0 (85.2, 100.0)	40	97.6 (87.1, 99.9)	70	94.6 (86.7, 98.5)	153	97.5 (93.6, 99.3)
False	0	0.0	1	2.4	1	1.4	3	1.9
I don't know	0	0.0	0	0.0	3	4.1	1	0.6

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	17	73.9 (51.6, 89.8)	32	78.0 (62.4, 89.4)	49	66.2 (54.3, 76.8)	116	73.9 (66.3, 80.6)
No	2	8.7	5	12.2	11	14.9	28	17.8
I don't know	4	17.4	4	9.8	14	18.9	13	8.3
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	23	100.0 (85.2,100.0)	41	100.0 (91.4,100.0)	74	100.0 (95.1,100.0)	156	99.4 (96.5,100.0)
No	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	1	0.6
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	21	91.3 (72.0, 98.9)	39	95.1 (83.5, 99.4)	67	90.5 (81.5, 96.1)	150	95.5 (91.0, 98.2)
False	1	4.3	0	0.0	5	6.8	4	2.5
I don't know	1	4.3	2	4.9	2	2.7	3	1.9

[1] Correct response

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	141	97.2 (93.1, 99.2)	87	96.7 (90.6, 99.3)	31	96.9 (83.8, 99.9)	14	93.3 (68.1, 99.8)
False	3	2.1	2	2.2	0	0.0	0	0.0
I don't know	1	0.7	1	1.1	1	3.1	1	6.7

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	109	75.2 (67.3, 82.0)	64	71.1 (60.6, 80.2)	22	68.8 (50.0, 83.9)	7	46.7 (21.3, 73.4)
No	19	13.1	16	17.8	5	15.6	7	46.7
I don't know	17	11.7	10	11.1	5	15.6	1	6.7
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	144	99.3 (96.2,100.0)	90	100.0 (96.0,100.0)	32	100.0 (89.1,100.0)	14	93.3 (68.1, 99.8)
No	0	0.0	0	0.0	0	0.0	0	0.0
I don't know	1	0.7	0	0.0	0	0.0	1	6.7
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	138	95.2 (90.3, 98.0)	83	92.2 (84.6, 96.8)	31	96.9 (83.8, 99.9)	14	93.3 (68.1, 99.8)
False	4	2.8	5	5.6	0	0.0	0	0.0
I don't know	3	2.1	2	2.2	1	3.1	1	6.7

[1] Correct response

TABLE 8.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

Demonstrated Understanding	Eligible and Complete Respondents N=300	
	N	%
0 correct responses	0	0.0
1 correct response	3	1.0
2 correct responses	7	2.3
3 correct responses	92	30.7
4 correct responses	198	66.0
Average number of correct responses	3.6	(3.4, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	3	1.1	0	0.0
2 correct responses	6	2.3	1	2.6
3 correct responses	75	28.6	17	44.7
4 correct responses	178	67.9	20	52.6
Average number of correct responses	3.6	(3.4, 4.0) [1]	3.5	(3.0, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	1.1	2	1.3	0	0.0
2 correct responses	3	3.3	3	2.0	1	2.1
3 correct responses	24	26.4	50	32.7	15	31.9
4 correct responses	63	69.2	98	64.1	31	66.0
Average number of correct responses	3.6	(3.3, 4.0)[1]	3.6	(3.3, 4.0)[1]	3.6	(3.2, 4.0)[1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=291		S-4b Telephone N=9	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	3	1.0	0	0.0
2 correct responses	7	2.4	0	0.0
3 correct responses	89	30.6	3	33.3
4 correct responses	192	66.0	6	66.7
Average number of correct responses	3.6	(3.4, 4.0) [1]	3.7	(2.6, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	1.4	1	0.6
2 correct responses	0	0.0	1	2.4	3	4.1	2	1.3
3 correct responses	8	34.8	10	24.4	27	36.5	46	29.3
4 correct responses	15	65.2	30	73.2	43	58.1	108	68.8
Average number of correct responses	3.7	(3.0, 4.0) [1]	3.7	(3.2, 4.0) [1]	3.5	(3.2, 4.0) [1]	3.7	(3.4, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	1	3.1	1	6.7
2 correct responses	3	2.1	4	4.4	0	0.0	0	0.0
3 correct responses	42	29.0	28	31.1	9	28.1	8	53.3
4 correct responses	100	69.0	58	64.4	22	68.8	6	40.0
Average number of correct responses	3.7	(3.4, 4.0) [1]	3.6	(3.3, 4.0) [1]	3.6	(3.1, 4.0) [1]	3.3	(2.5, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

Question	Eligible and Complete Respondents N=300	
	N	% (95% CI) [2]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
False [1]	284	94.7 (91.5, 96.9)
True	6	2.0
I don't know	10	3.3
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True [1]	276	92.0 (88.3, 94.8)
False	5	1.7
I don't know	19	6.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True [1]	274	91.3 (87.6, 94.3)
False	10	3.3
I don't know	16	5.3

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	250	95.4 (92.1, 97.6)	34	89.5 (75.2, 97.1)
True	6	2.3	0	0.0
I don't know	6	2.3	4	10.5
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	242	92.4 (88.5, 95.3)	34	89.5 (75.2, 97.1)
False	3	1.1	2	5.3
I don't know	17	6.5	2	5.3

Question	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	245	93.5 (89.8, 96.2)	29	76.3 (59.8, 88.6)
False	6	2.3	4	10.5
I don't know	11	4.2	5	13.2

[1] Correct response

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Question	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.						
10b: TIRF medicines are interchangeable with each other regardless of route of administration.						
False [1]	84	92.3 (84.8, 96.9)	147	96.1 (91.7, 98.5)	44	93.6 (82.5, 98.7)
True	5	5.5	0	0.0	1	2.1
I don't know	2	2.2	6	3.9	2	4.3
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.						
True [1]	83	91.2 (83.4, 96.1)	141	92.2 (86.7, 95.9)	43	91.5 (79.6, 97.6)
False	2	2.2	1	0.7	2	4.3
I don't know	6	6.6	11	7.2	2	4.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
True [1]	80	87.9 (79.4, 93.8)	146	95.4 (90.8, 98.1)	39	83.0 (69.2, 92.4)
False	6	6.6	3	2.0	1	2.1
I don't know	5	5.5	4	2.6	7	14.9

[1] Correct response

TABLE 9.1.4 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Question	S-4a Internet N=291		S-4b Telephone N=9	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	275	94.5 (91.2, 96.8)	9	100.0 (66.4, 100.0)
True	6	2.1	0	0.0
I don't know	10	3.4	0	0.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	267	91.8 (88.0, 94.6)	9	100.0 (66.4, 100.0)
False	5	1.7	0	0.0
I don't know	19	6.5	0	0.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	265	91.1 (87.2, 94.1)	9	100.0 (66.4, 100.0)
False	10	3.4	0	0.0
I don't know	16	5.5	0	0.0

[1] Correct response

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	20	87.0 (66.4, 97.2)	38	92.7 (80.1, 98.5)	69	93.2 (84.9, 97.8)	152	96.8 (92.7, 99.0)
True	1	4.3	1	2.4	2	2.7	2	1.3
I don't know	2	8.7	2	4.9	3	4.1	3	1.9

Question	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	20	87.0 (66.4, 97.2)	39	95.1 (83.5, 99.4)	64	86.5 (76.5, 93.3)	149	94.9 (90.2, 97.8)
False	1	4.3	0	0.0	1	1.4	3	1.9
I don't know	2	8.7	2	4.9	9	12.2	5	3.2
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	20	87.0 (66.4, 97.2)	39	95.1 (83.5, 99.4)	65	87.8 (78.2, 94.3)	146	93.0 (87.8, 96.5)
False	0	0.0	0	0.0	4	5.4	6	3.8
I don't know	3	13.0	2	4.9	5	6.8	5	3.2

[1] Correct response

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	136	93.8 (88.5, 97.1)	89	98.9 (94.0, 100.0)	31	96.9 (83.8, 99.9)	13	86.7 (59.5, 98.3)
True	3	2.1	1	1.1	0	0.0	1	6.7
I don't know	6	4.1	0	0.0	1	3.1	1	6.7

Question	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	133	91.7 (86.0, 95.7)	85	94.4 (87.5, 98.2)	31	96.9 (83.8, 99.9)	12	80.0 (51.9, 95.7)
False	1	0.7	1	1.1	0	0.0	1	6.7
I don't know	11	7.6	4	4.4	1	3.1	2	13.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	133	91.7 (86.0, 95.7)	86	95.6 (89.0, 98.8)	29	90.6 (75.0, 98.0)	12	80.0 (51.9, 95.7)
False	4	2.8	1	1.1	2	6.3	2	13.3
I don't know	8	5.5	3	3.3	1	3.1	1	6.7

[1] Correct response

TABLE 9.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

Demonstrated Understanding	Eligible and Complete Respondents N=300	
	N	%
0 correct responses	5	1.7
1 correct response	11	3.7
2 correct responses	29	9.7
3 correct responses	255	85.0
Average number of correct responses	2.8	(2.6, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 18, 19, 20 AND 21):

- **S-1a-Respondents who read the Full Prescribing Information (Question 19) and Medication Guide for the TIRF medicine that they dispense (Question 21).**
- **S-1b-Respondents who responded "No" or "I don't know" to getting and reading the Full Prescribing Information and to getting and reading the Medication Guide for the TIRF medicine that they dispense.**

Demonstrated Understanding	S-1a Read Medication Guide or Full Prescribing Info N=262		S-1b Did not read Medication Guide and Full Prescribing Info N=38	
	N	%	N	%
0 correct responses	3	1.1	2	5.3
1 correct response	9	3.4	2	5.3
2 correct responses	22	8.4	7	18.4
3 correct responses	228	87.0	27	71.1
Average number of correct responses	2.8	(2.6, 3.0) [1]	2.6	(2.1, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: TIME TO COMPLETE SURVEY – INTERNET:

- **S-2a - <10 min**
- **S-2b – 10 to <20 min**
- **S-2c – ≥ 20 min**

Demonstrated Understanding	S-2a <10 min N=91		S-2b 10 to <20 min N=153		S-2c >= 20 min N=47	
	N	%	N	%	N	%
0 correct responses	2	2.2	2	1.3	1	2.1
1 correct response	3	3.3	4	2.6	4	8.5
2 correct responses	14	15.4	11	7.2	4	8.5
3 correct responses	72	79.1	136	88.9	38	80.9
Average number of correct responses	2.7	(2.4, 3.0) [1]	2.8	(2.6, 3.0) [1]	2.7	(2.3, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.2.4 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 4: MODALITY TO COMPLETE SURVEY:

- **S-4a - Internet**
- **S-4b - Telephone**

Demonstrated Understanding	S-4a Internet N=291		S-4b Telephone N=9	
	N	%	N	%
0 correct responses	5	1.7	0	0.0
1 correct response	11	3.8	0	0.0
2 correct responses	29	10.0	0	0.0
3 correct responses	246	84.5	9	100.0
Average number of correct responses	2.8	(2.6, 3.0) [1]	3.0	(2.1, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 5: TIME PRACTICING AS A PHARMACIST (QUESTION 28):

- **S-5a - Less than 3 years**
- **S-5b – 3 to 5 years**
- **S-5c – 6 to 15 years**
- **S-5d – More than 15 years**

Demonstrated Understanding	S-5a Less than 3 years N=23		S-5b 3 to 5 years N=41		S-5c 6 to 15 years N=74		S-5d More than 15 years N=157	
	N	%	N	%	N	%	N	%
0 correct responses	1	4.3	0	0.0	2	2.7	2	1.3
1 correct response	3	13.0	1	2.4	3	4.1	3	1.9
2 correct responses	0	0.0	5	12.2	12	16.2	12	7.6
3 correct responses	19	82.6	35	85.4	57	77.0	140	89.2
Average number of correct responses	2.6	(2.1, 3.0) [1]	2.8	(2.4, 3.0) [1]	2.7	(2.4, 3.0) [1]	2.8	(2.6, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: NUMBER OF TIMES PER MONTH DISPENSED TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 25):

- **S-6a - None**
- **S-6b - 1 - 2 times per month**
- **S-6c - 3 - 5 times per month**
- **S-6d - More than 5 times per month**

Demonstrated Understanding	S-6a None N=145		S-6b 1 - 2 N=90		S-6c 3 - 5 N=32		S-6d More than 5 N=15	
	N	%	N	%	N	%	N	%
0 correct responses	2	1.4	0	0.0	1	3.1	1	6.7
1 correct response	4	2.8	2	2.2	0	0.0	2	13.3
2 correct responses	19	13.1	6	6.7	2	6.3	1	6.7
3 correct responses	120	82.8	82	91.1	29	90.6	11	73.3
Average number of correct responses	2.8	(2.5, 3.0) [1]	2.9	(2.6, 3.0) [1]	2.8	(2.4, 3.0) [1]	2.5	(1.8, 3.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

Appendix C Findings Report: Qualitative Research to Evaluate the Prescriber and Pharmacist 12-month REMS Assessment Surveys for TIRF Medicines

Findings Report:
Qualitative Research to Evaluate the Prescriber and Pharmacist 12-month REMS Assessment Surveys for Transmucosal Immediate Release Fentanyl (TIRF) Medicines

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16 December 2013
Version 3.0

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TABLE OF CONTENTS

1 INTRODUCTION

The Food and Drug Administration (FDA) has approved a shared risk evaluation and mitigation strategy (REMS) for the class of transmucosal immediate-release fentanyl (TIRF) products. The products in the TIRF REMS Program include ABSTRAL® (fentanyl) sublingual tablets CII, ACTIQ® (fentanyl citrate) oral transmucosal lozenge CII, FENTORA® (fentanyl buccal tablet) CII, LAZANDA® (fentanyl) nasal spray CII, and ONSOLIS® (fentanyl buccal soluble film) CII, SUBSYS® (fentanyl) sublingual spray CII, as well as generic forms of the aforementioned products.

The FDA provided feedback to the TIRF REMS Industry Group (TRIG) on the Knowledge, Attitude, and Behavior survey results for prescribers and pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions. The research undertaken included review of the questions identified by the FDA that had low correct response rates, as well as two new questions approved by the TRIG. This document describes how this research was conducted, including a description of research participants, and major findings used to inform KAB survey revisions.

2 RESEARCH OBJECTIVES

The purpose of this qualitative research was to investigate the causes for low correct response rates to specific prescriber and pharmacist questions used in the survey administered as part of the TIRF REMS Access Program 12-month REMS Assessment. Additionally, this research was conducted to assess proposed revised wording to select questions, as well as to assess comprehension of two additional questions.

The questions reviewed during the qualitative research interviews included the following (see Appendix A for full question sets. Readers should note that the survey content that is displayed in blue font represents proposed revised wording.):

- Prescribers reviewed:
  - 10 items from the Prescriber 12-month REMS Assessment Survey Questions: 5a, 5c, 8e, 11b, 12c, 12d, 15a-d
  - New questions 7 and 19
- Pharmacists reviewed:
  - 7 items from the Pharmacist 12-month REMS Assessment Survey Questions: 5a, 5c, 8 (a-e);
  - New question 7

The objectives of this research were to:

- Evaluate clarity and comprehension of questions and answer options used in the 12-month assessment;
- Identify terms, questions or topics for clarification or revision based on any areas of confusion with or misunderstanding for current wording;
- Determine how participants understand specific questions and why those questions are answered a particular way;
- Determine how certain questions might be understood differently and answered more accurately if further clarified;
- Evaluate alternative language for these questions.

3 RESEARCH DESIGN

3.1 OVERVIEW

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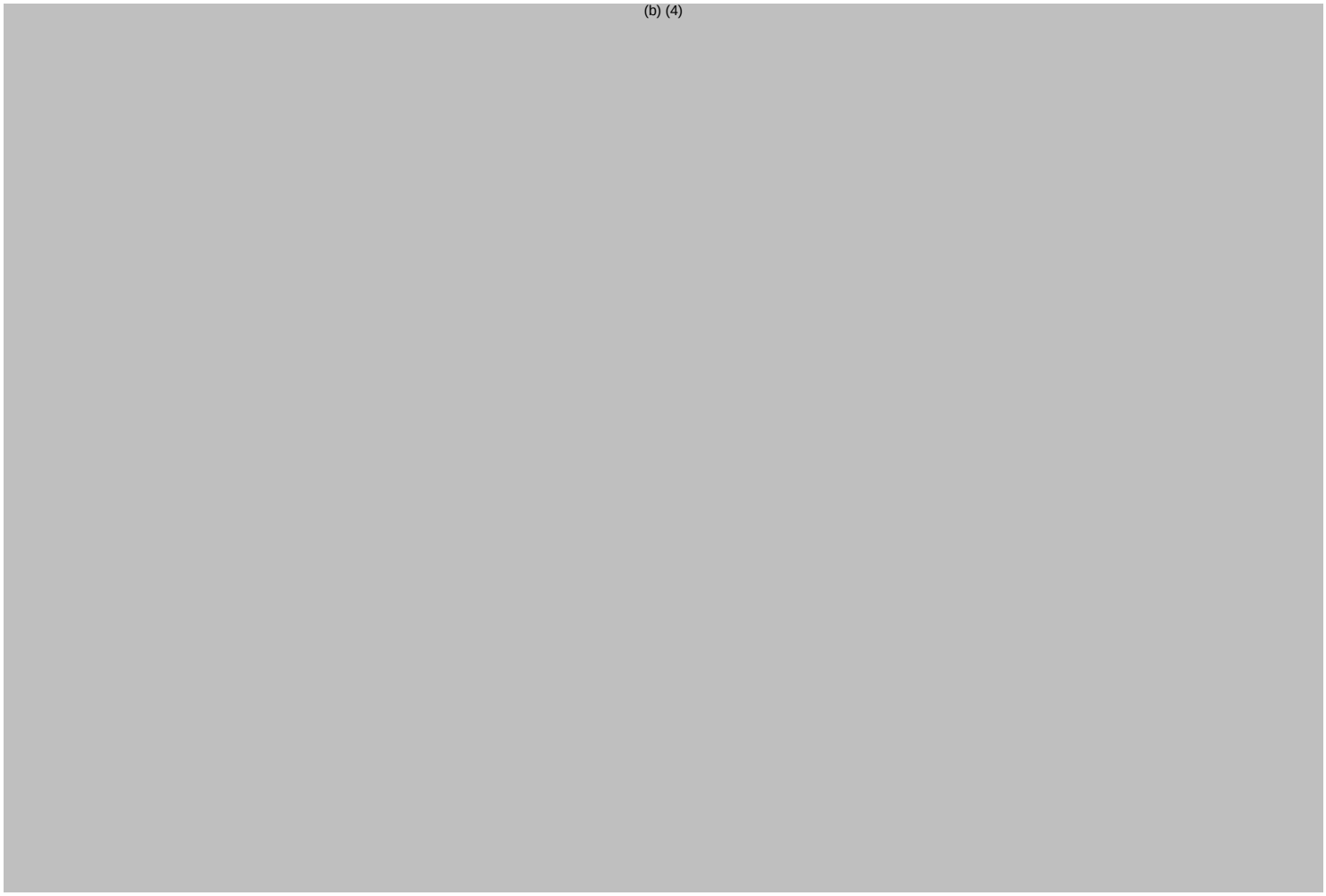

3.2 ELIGIBILITY CRITERIA

(b) (4)

3.3 RECRUITMENT

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3.4 PARTICIPANT DEMOGRAPHICS

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4 INTERVIEW DESIGN

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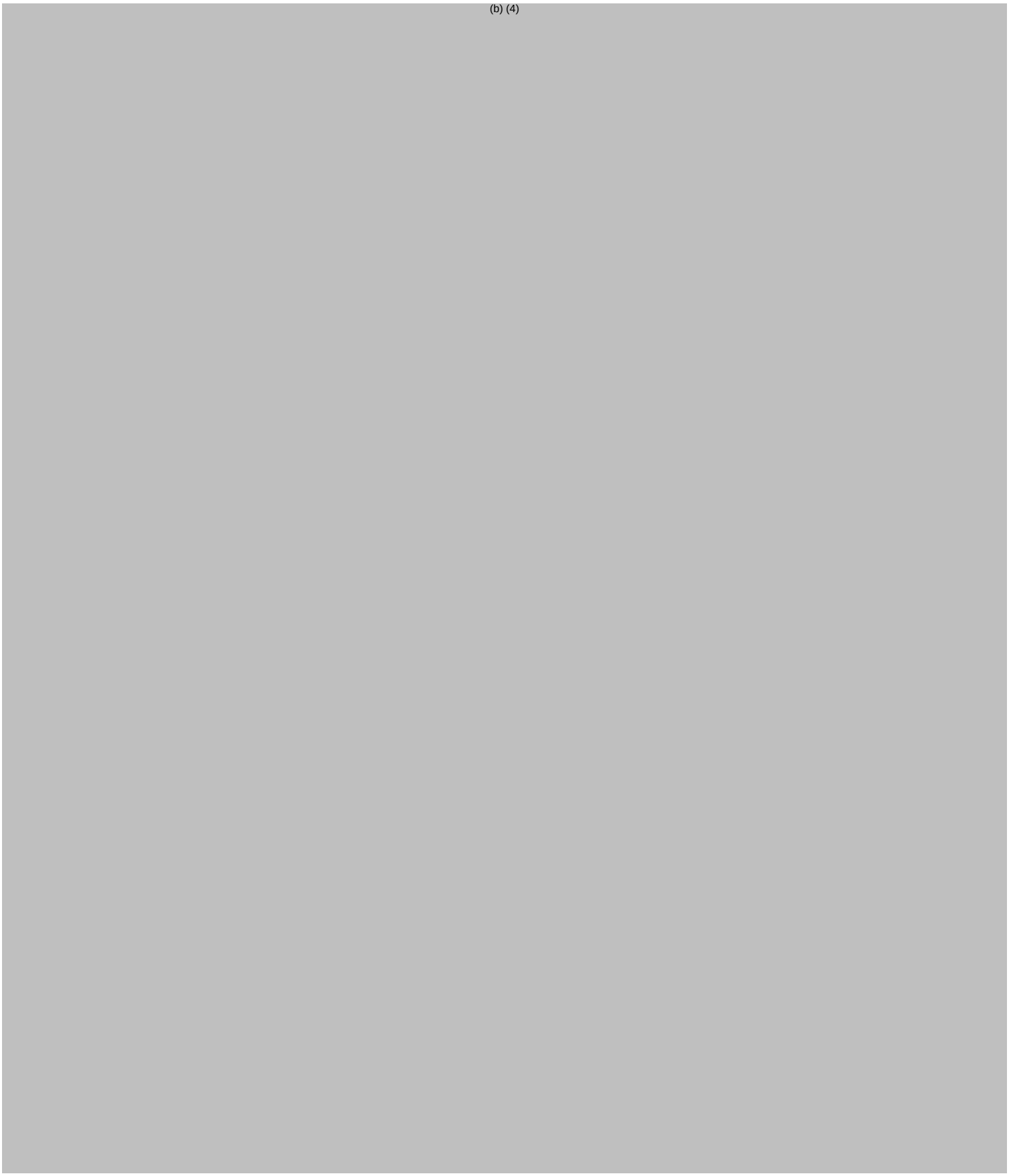

5 RESEARCH FINDINGS

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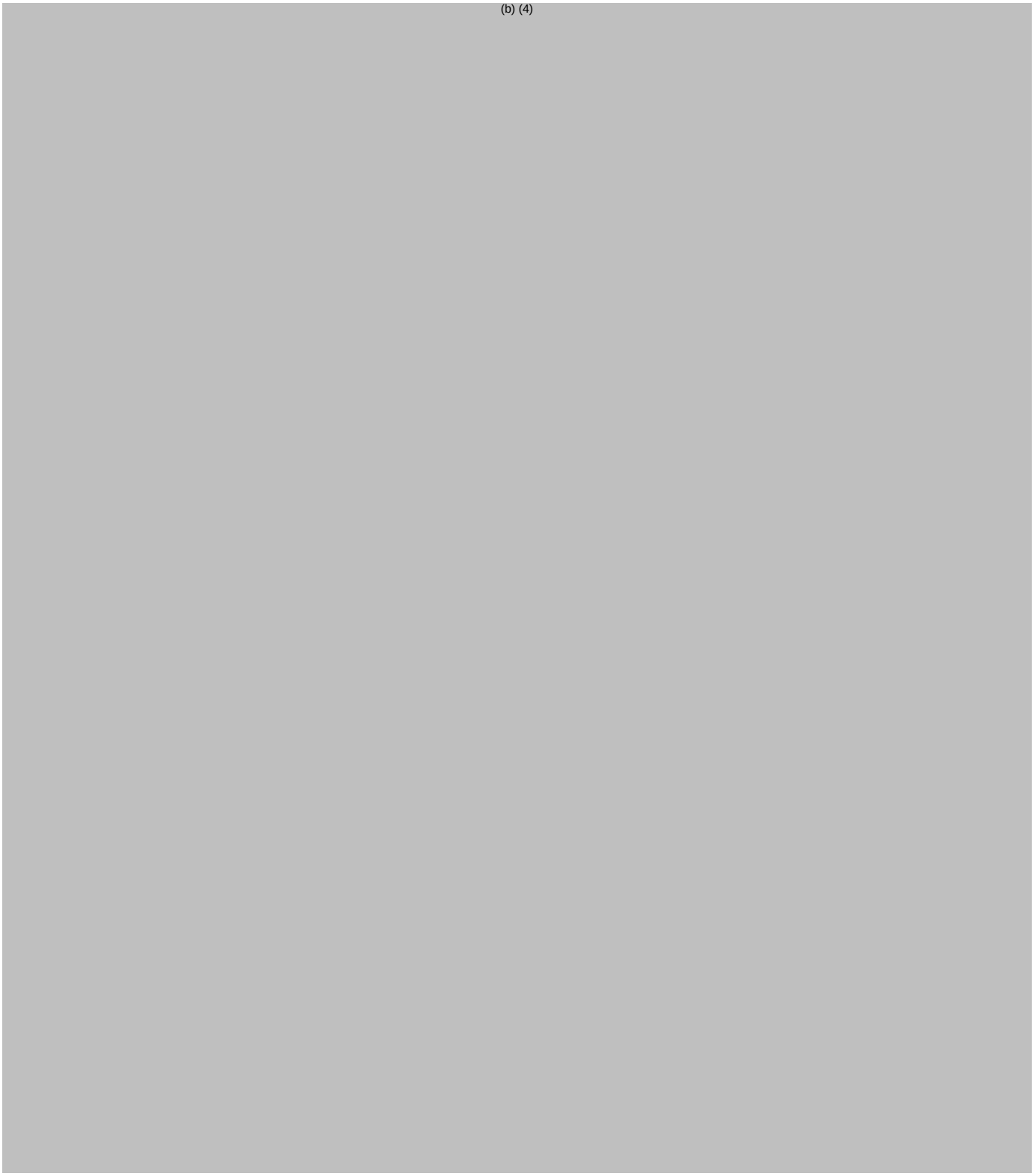

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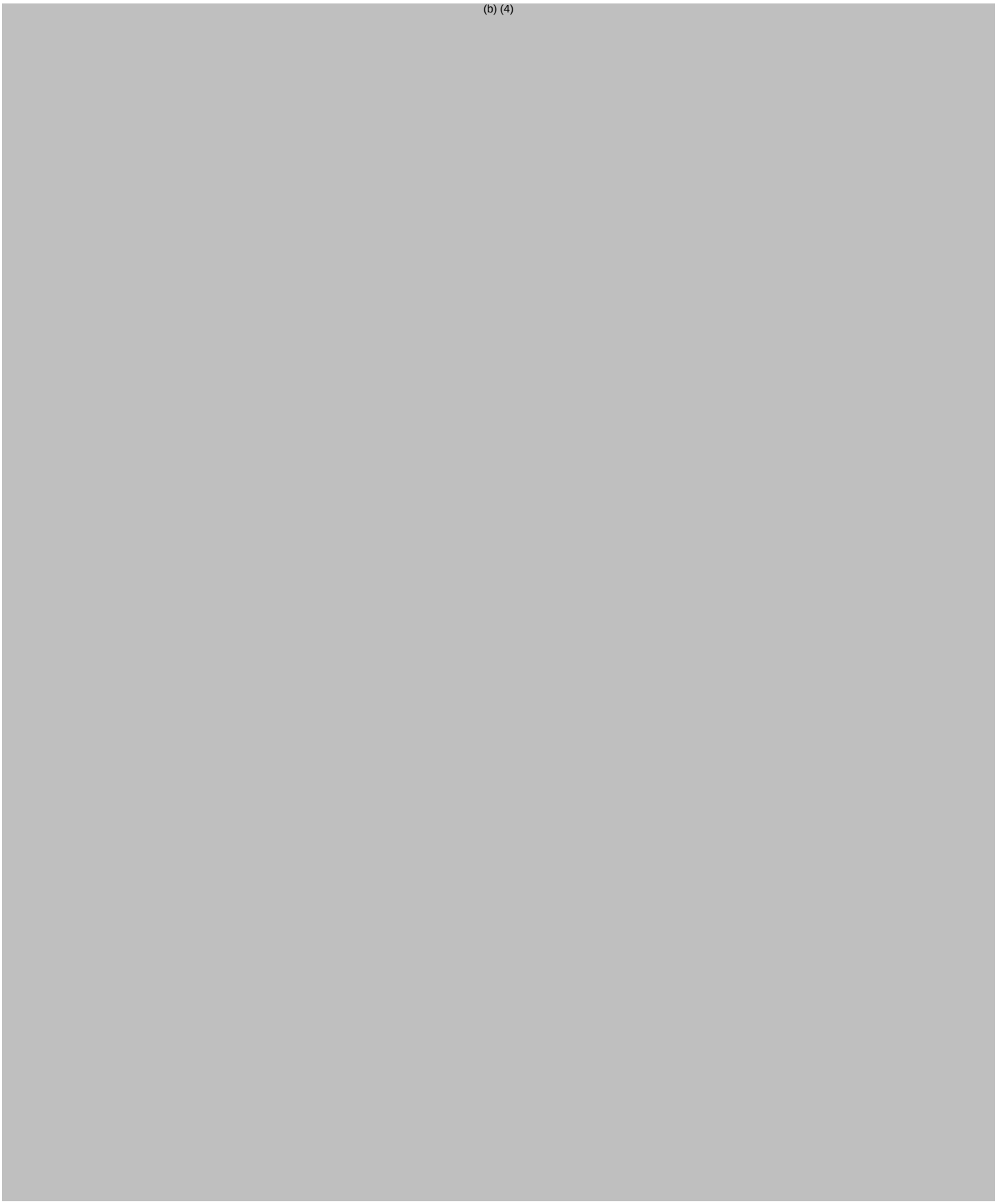

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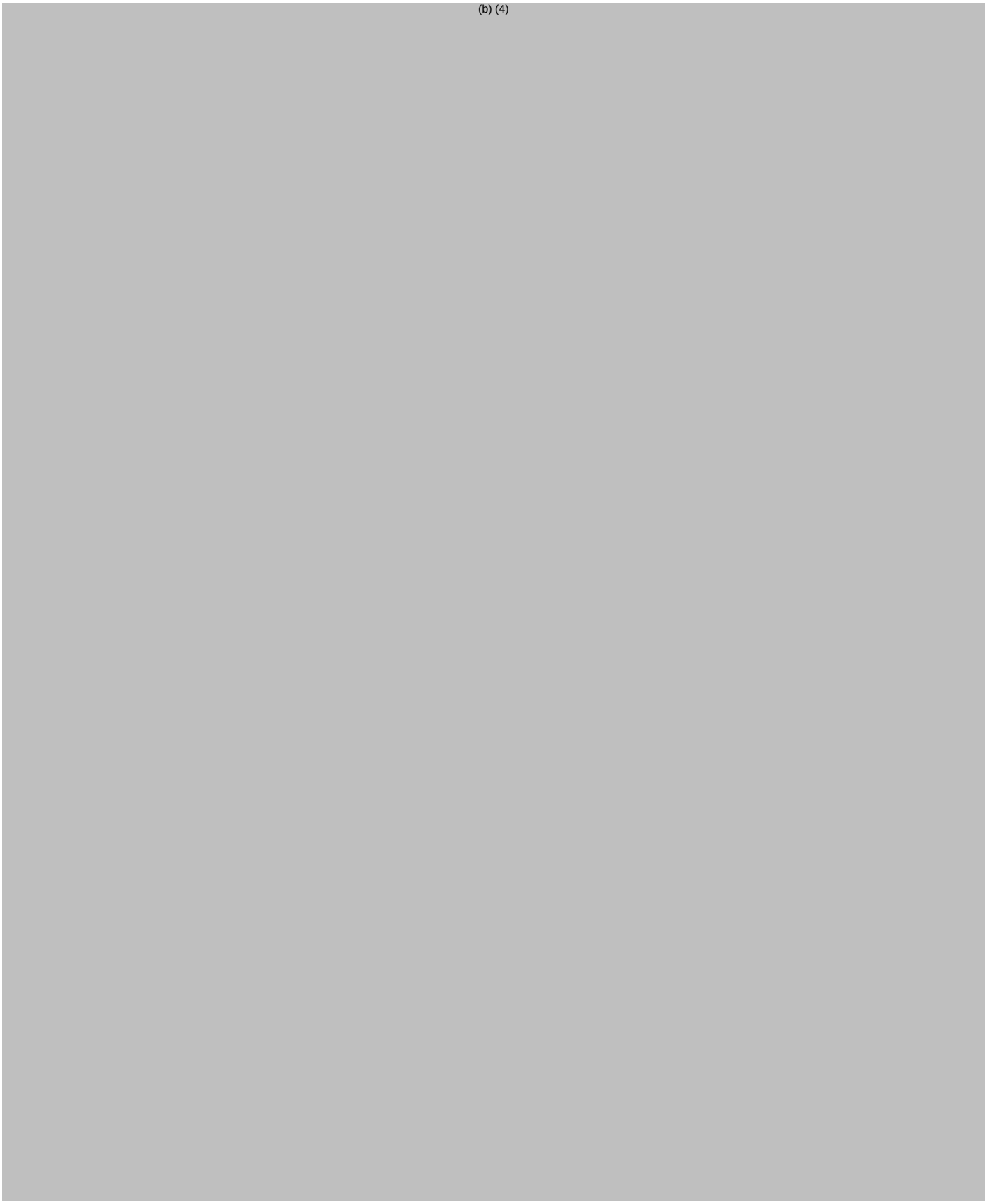

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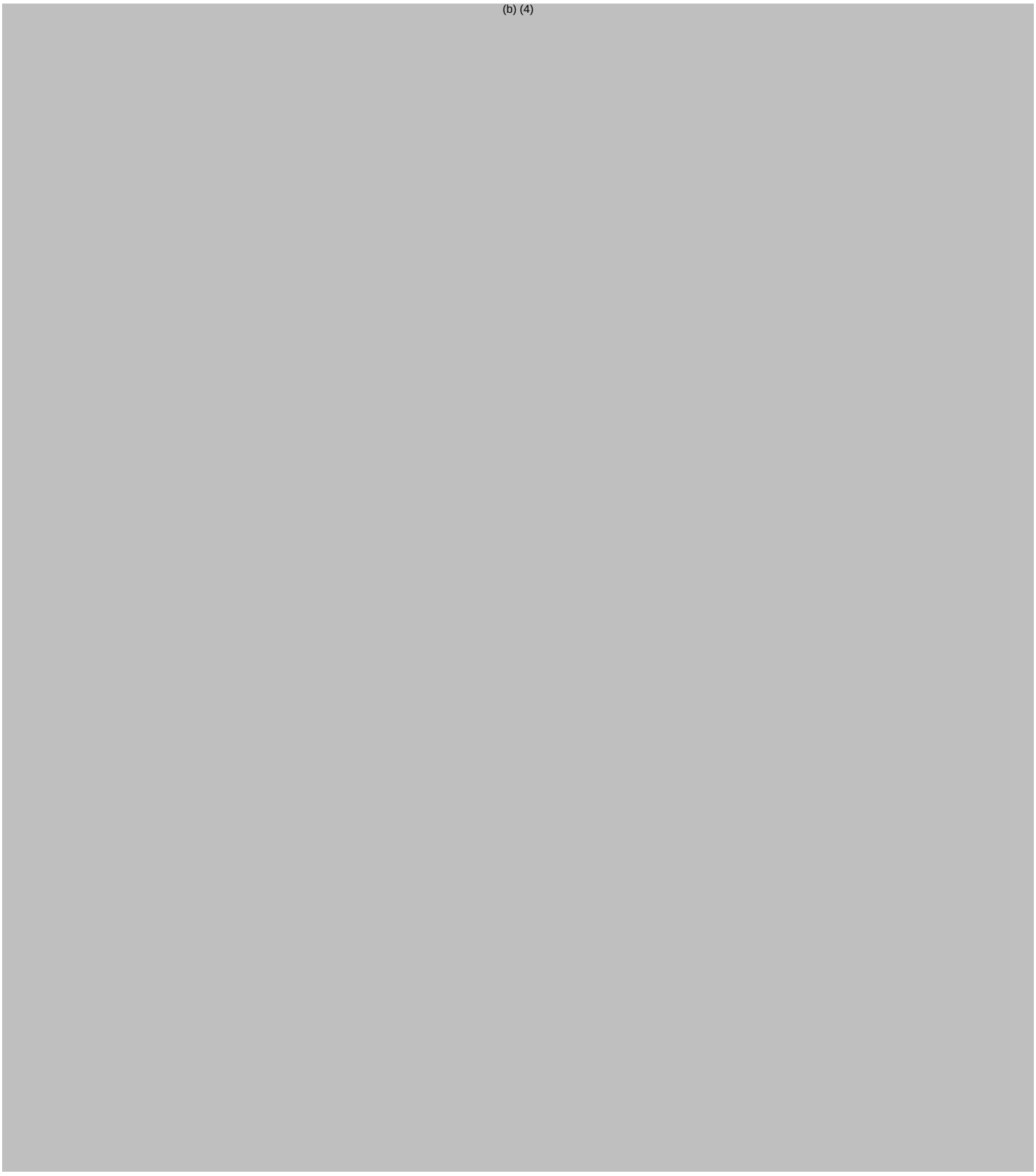

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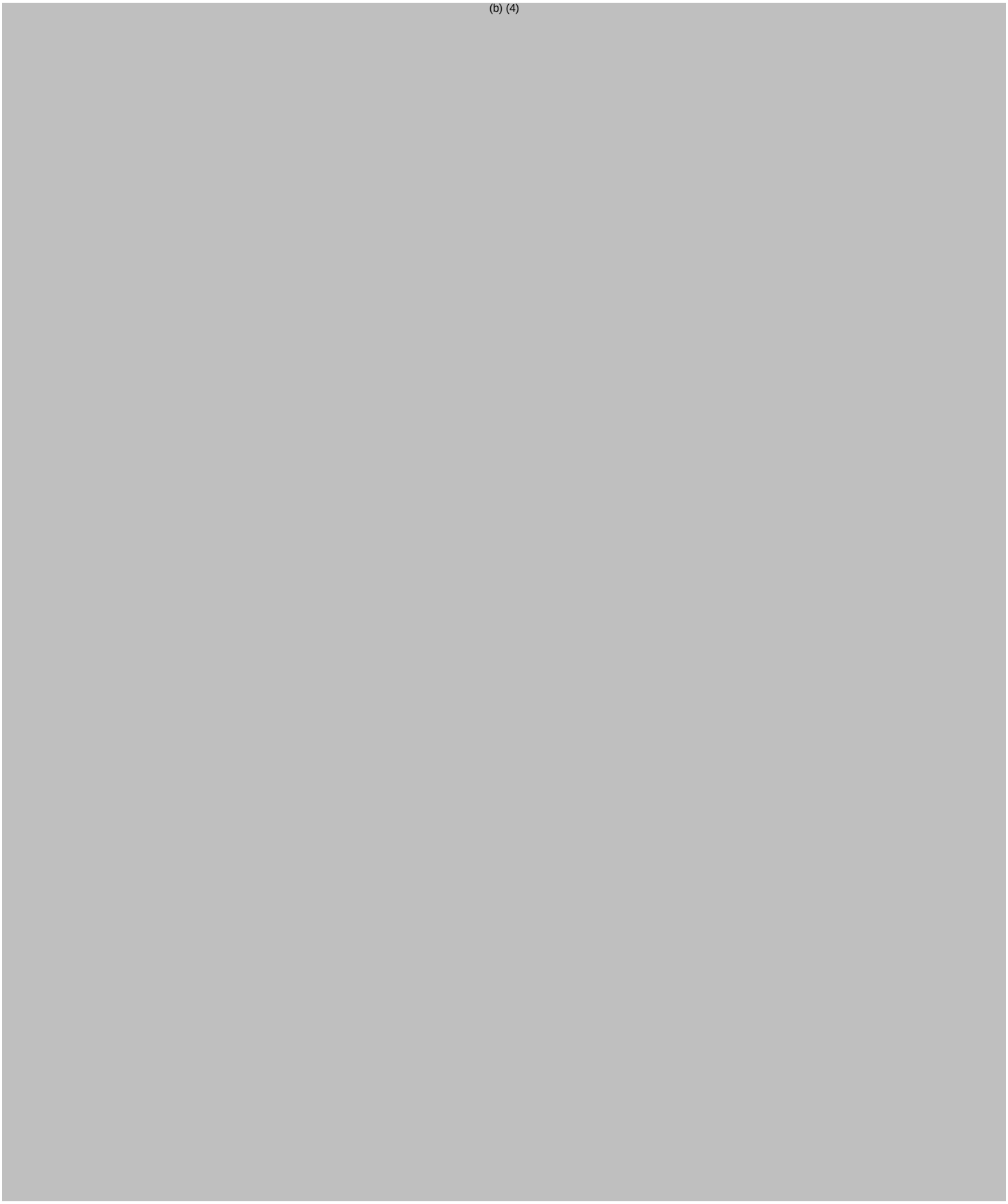

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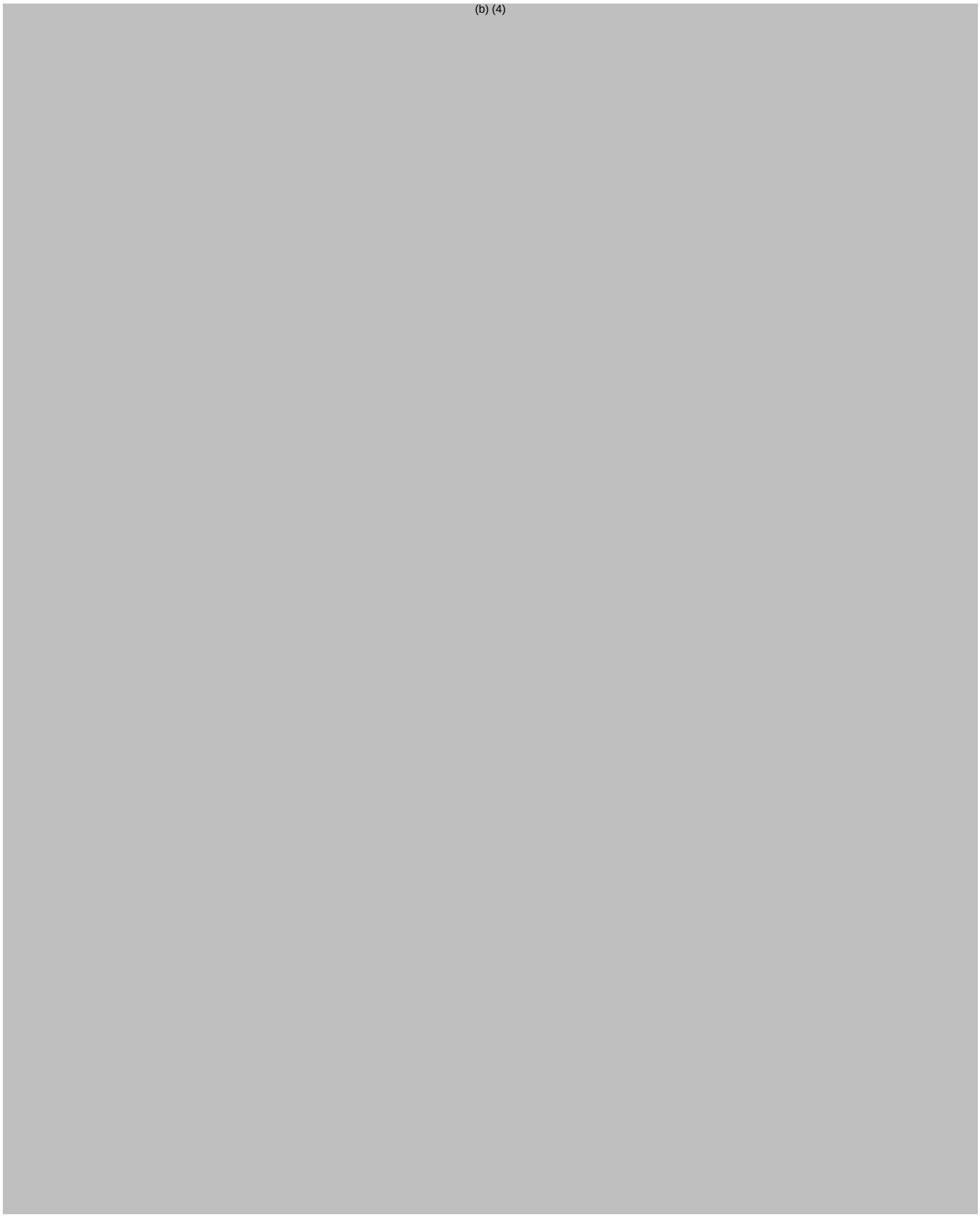

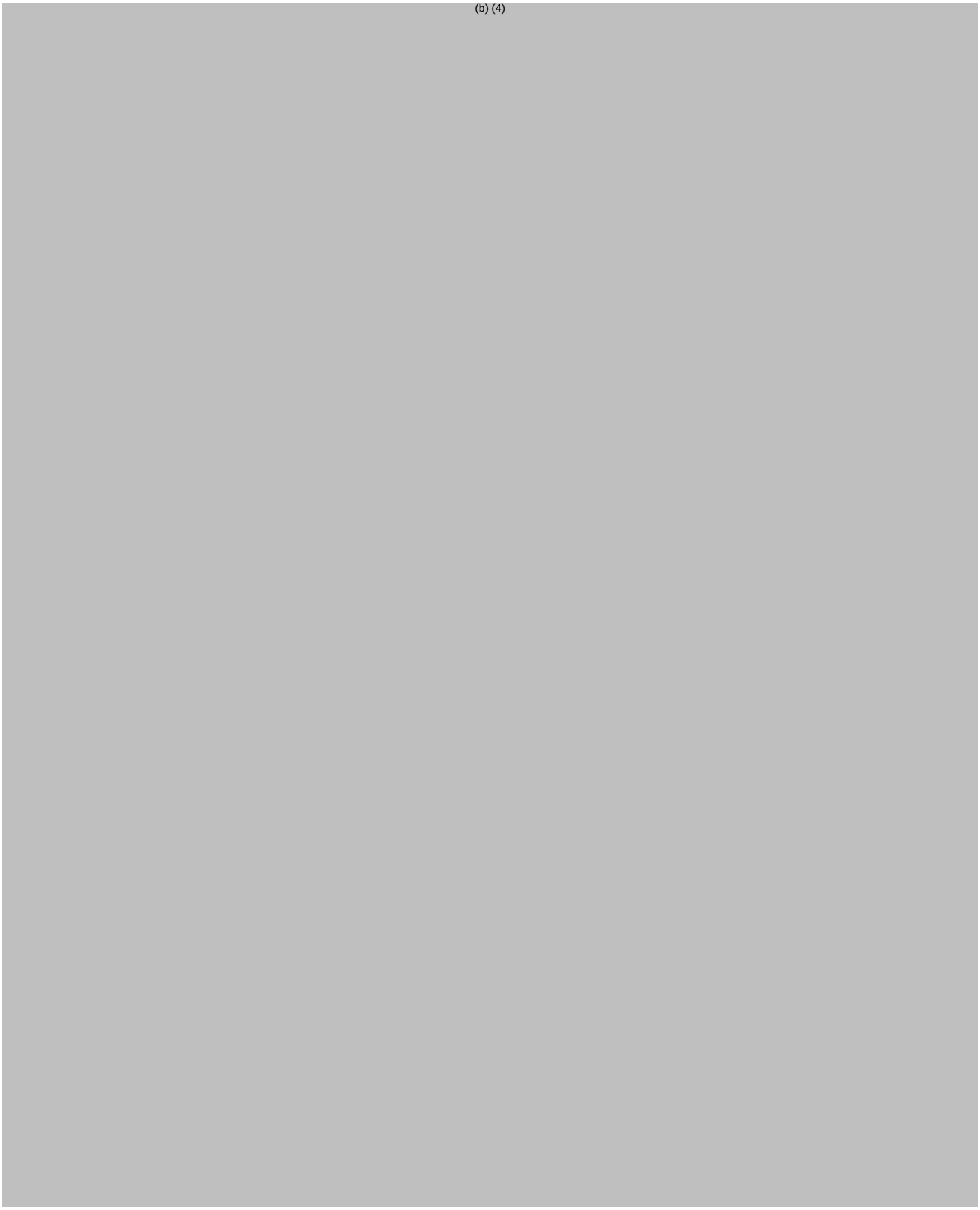
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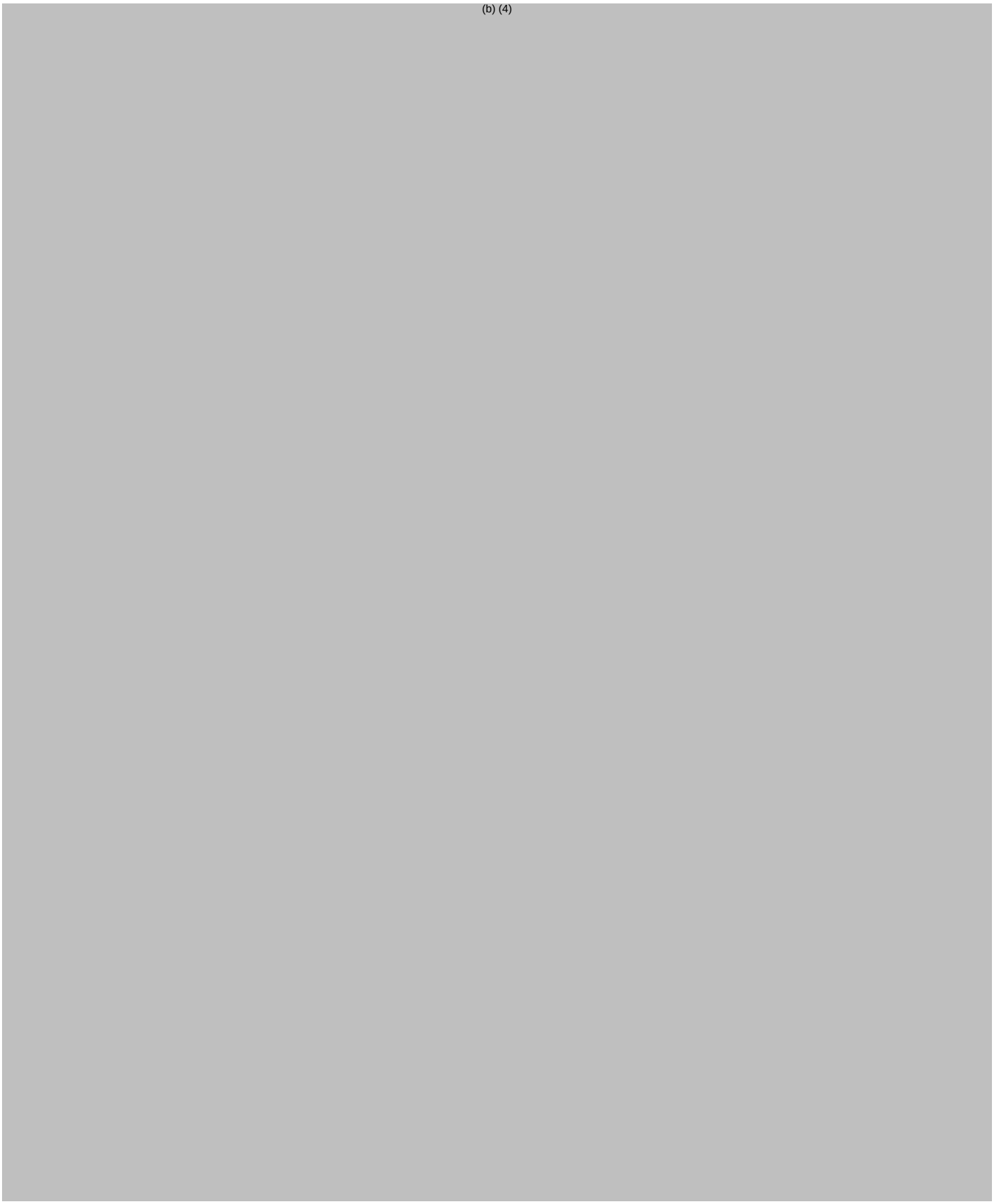

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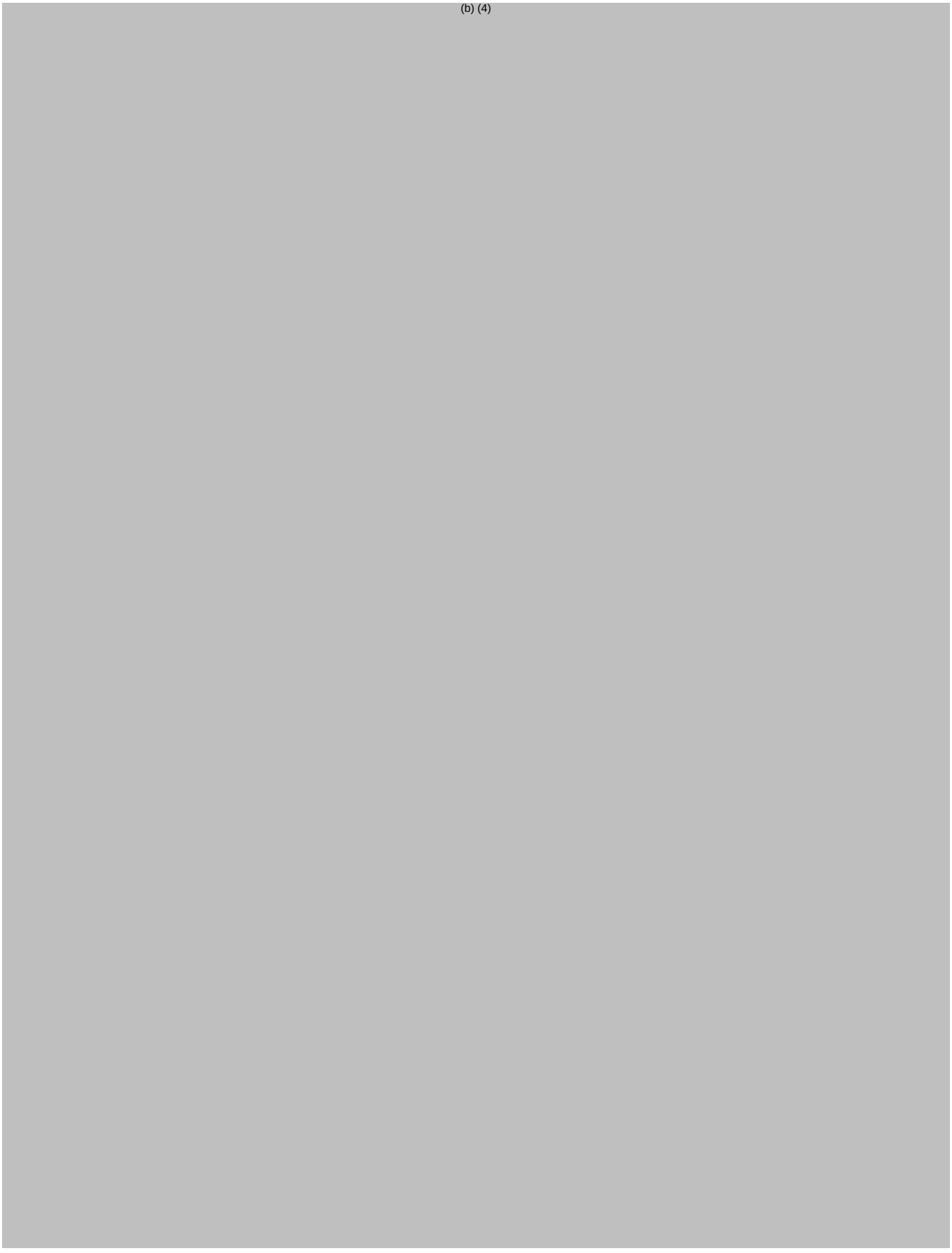

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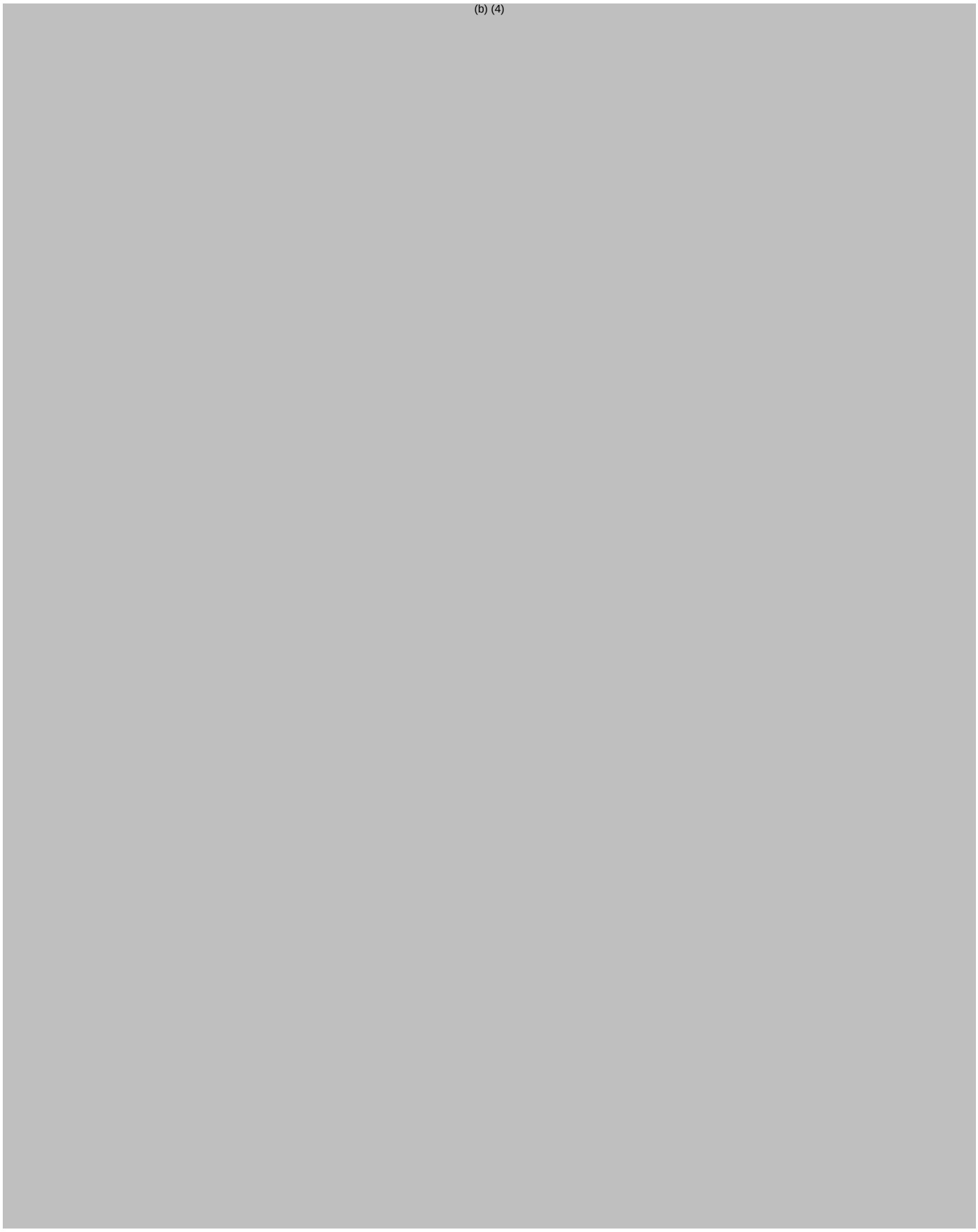

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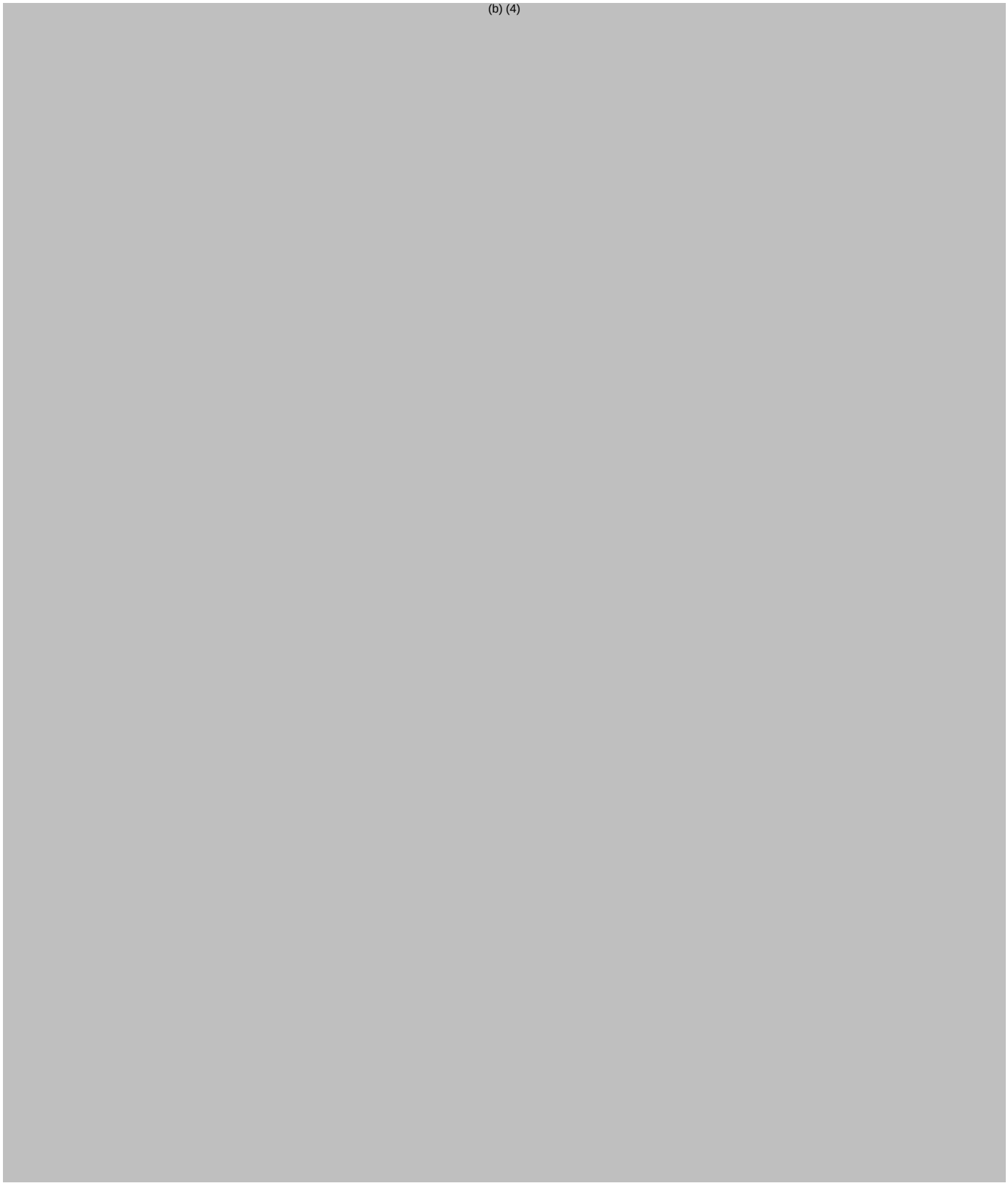
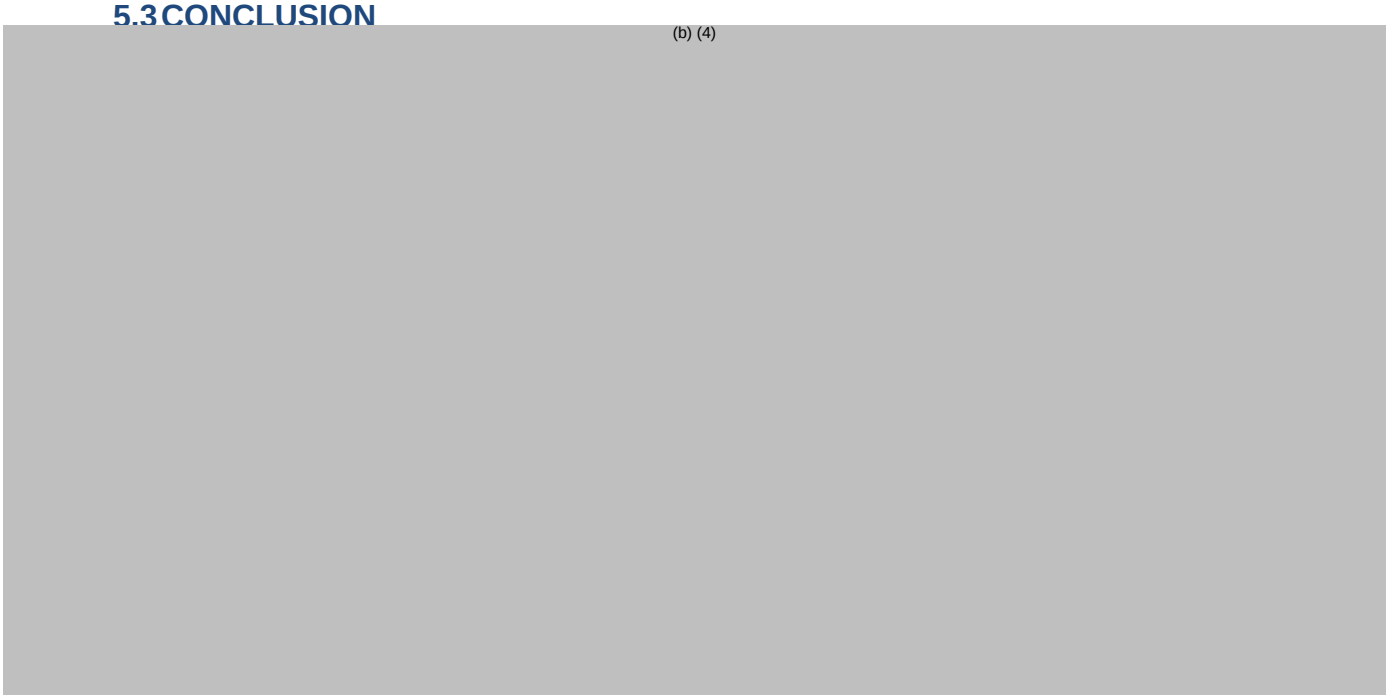


5.3 CONCLUSION

(b) (4)



6 APPENDIX A: SURVEY QUESTIONS USED IN QUALITATIVE RESEARCH

The following survey questions were studied during the qualitative research interviews. A hard copy was sent to each participant as appropriate by stakeholder and returned to the research facility after the interviews were completed. Readers should note that survey content displayed in blue font represents alternative survey questions/responses developed for this research.

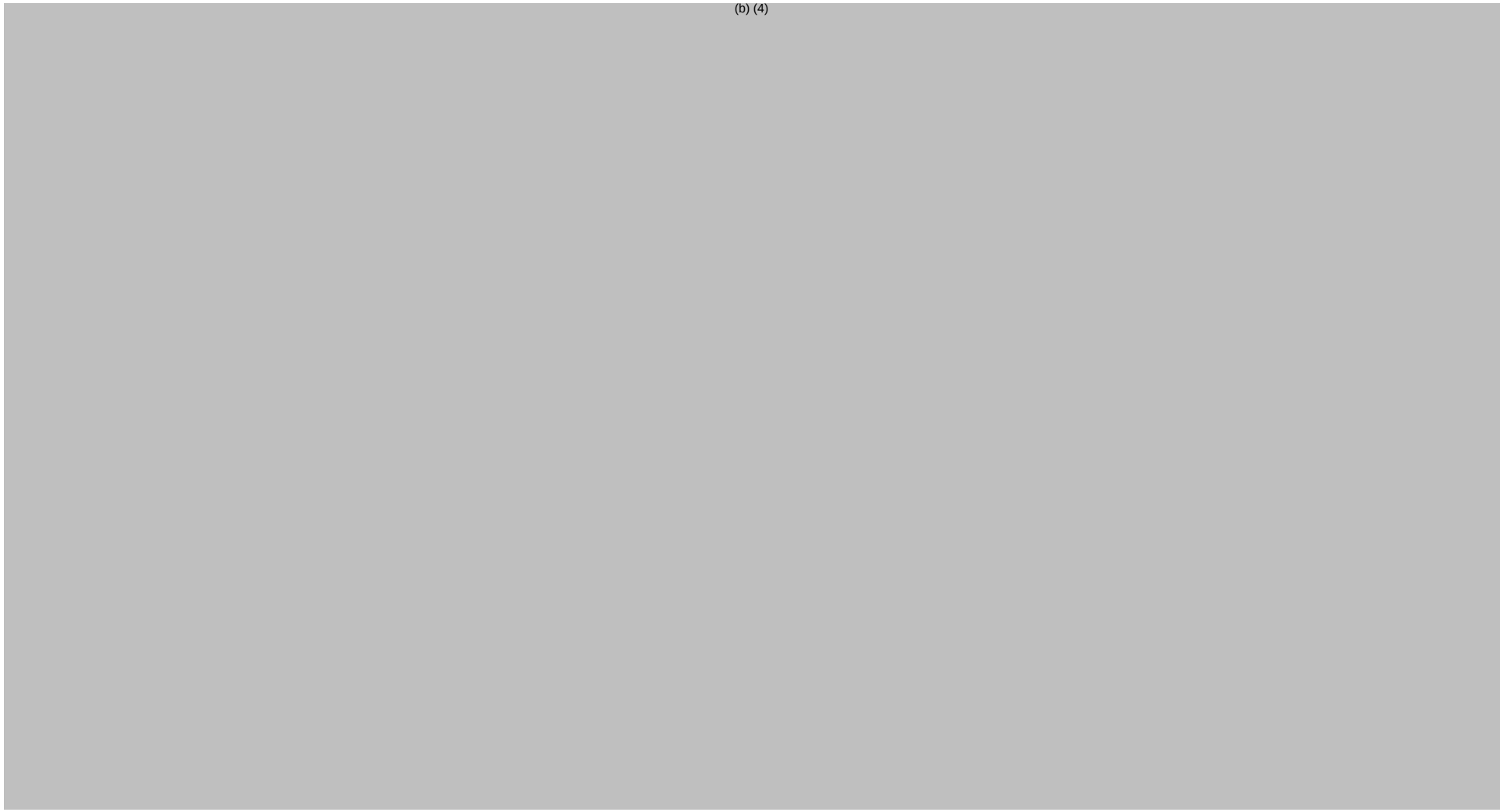
FDA_1292

TIRF Medicines Prescriber Survey

The Moderator will review the enclosed questions with you during the interview.

Please do not fill in the answer choices.

This document is only meant to guide your discussion with the Moderator.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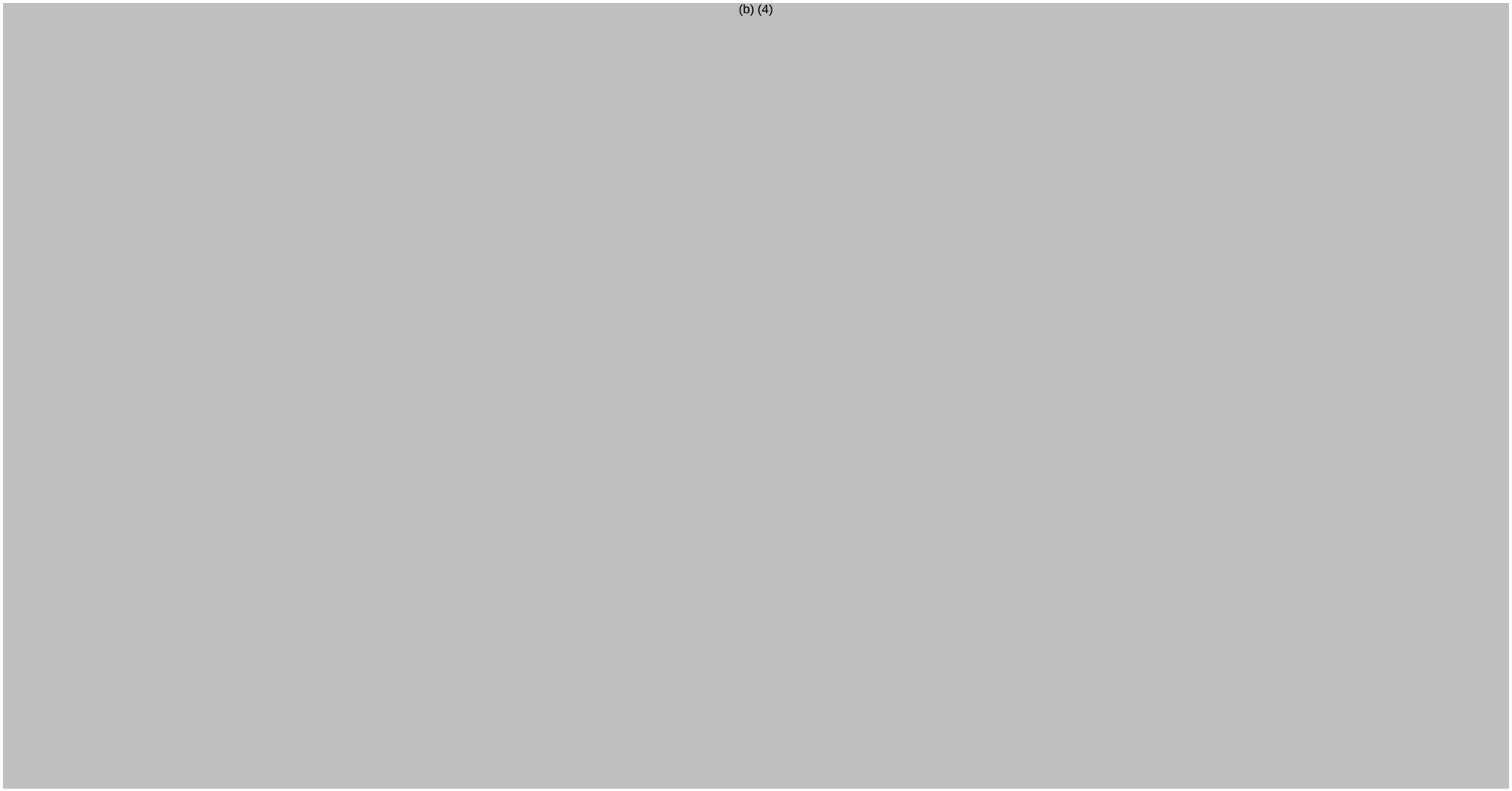
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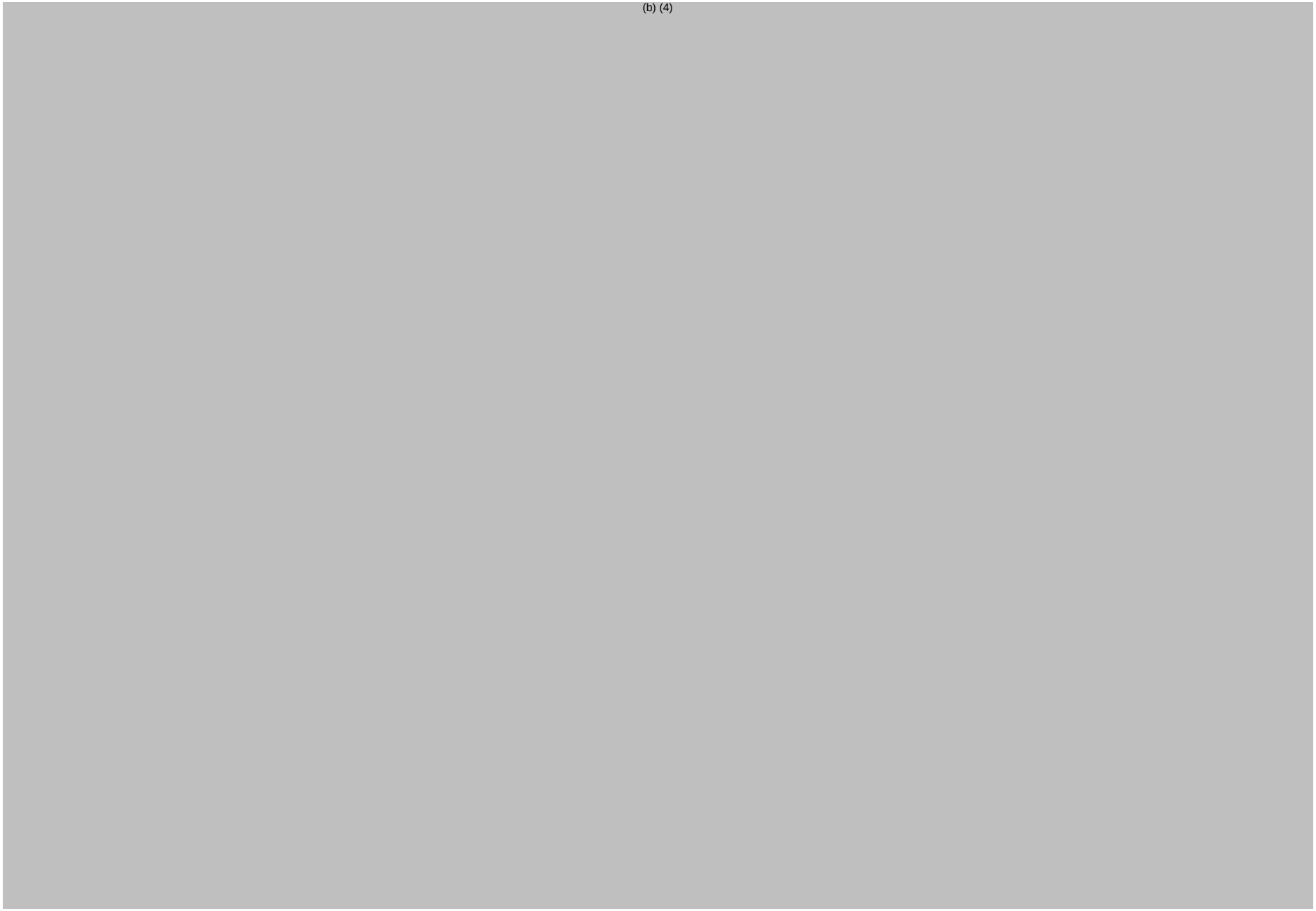
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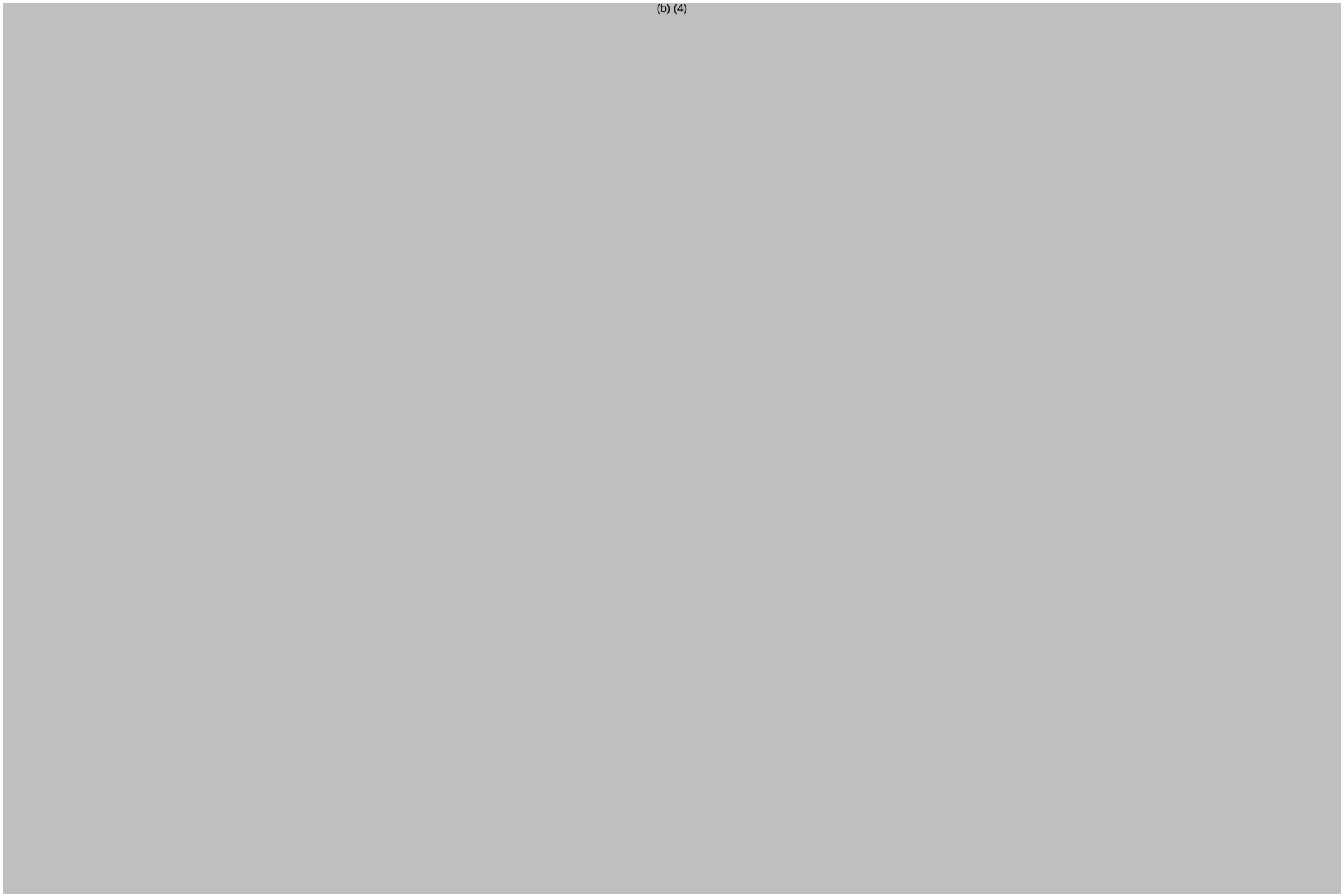
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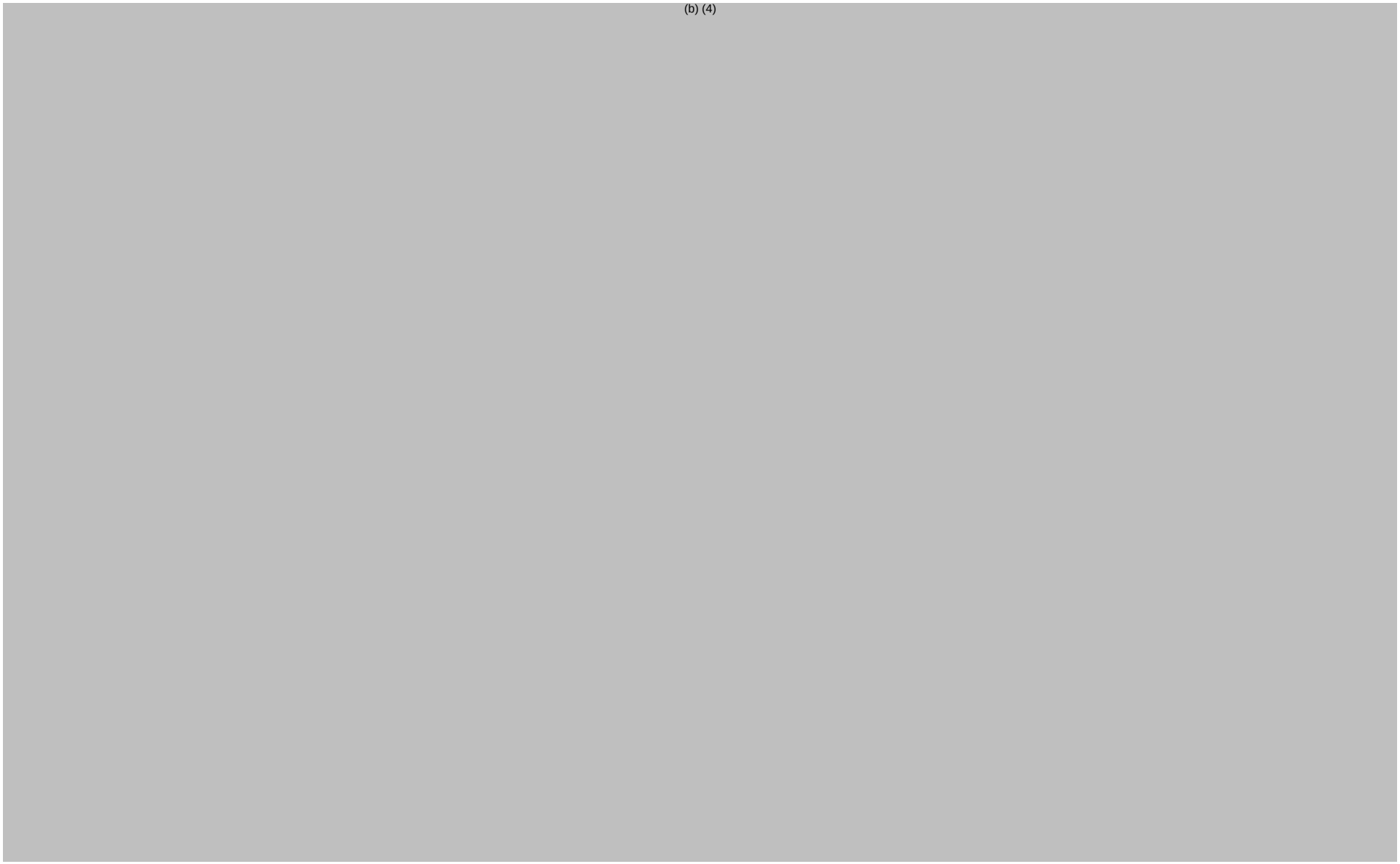
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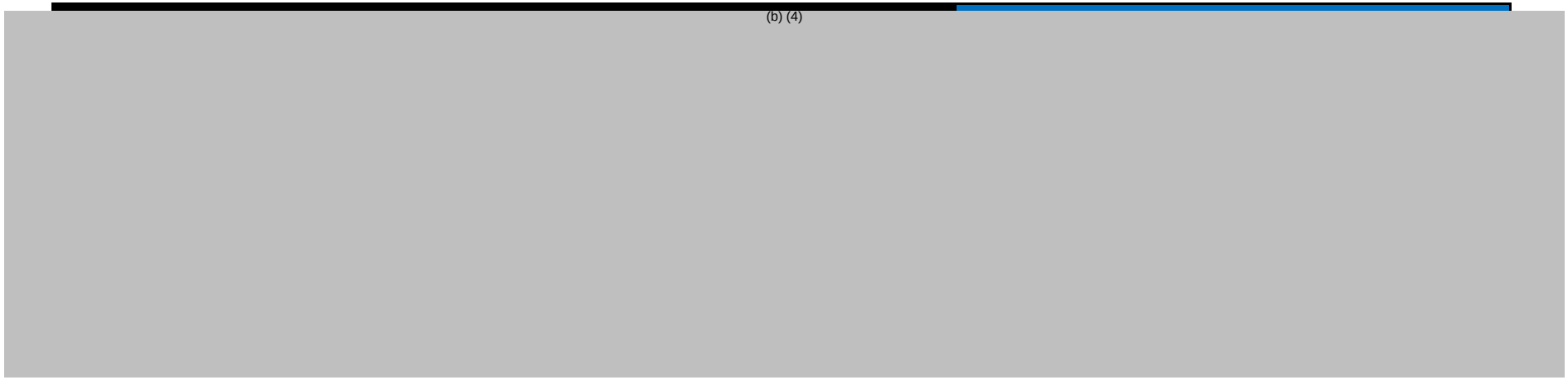
(b) (4)

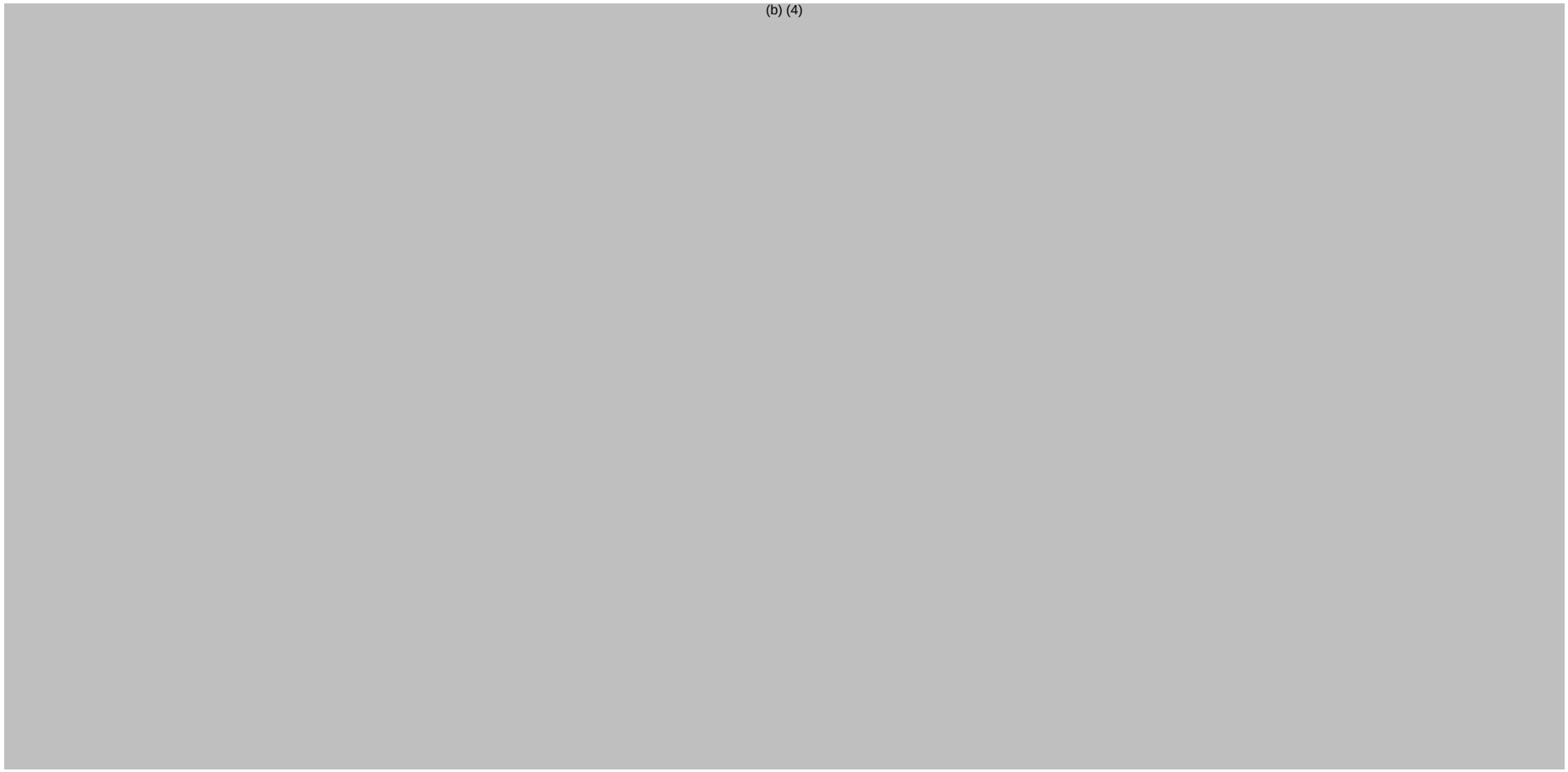

(b) (4)

TIRF Medicines Pharmacist Survey

The Moderator will review the enclosed questions with you during the interview.

Please do not fill in the answer choices.

This document is only meant to guide your discussion with the Moderator.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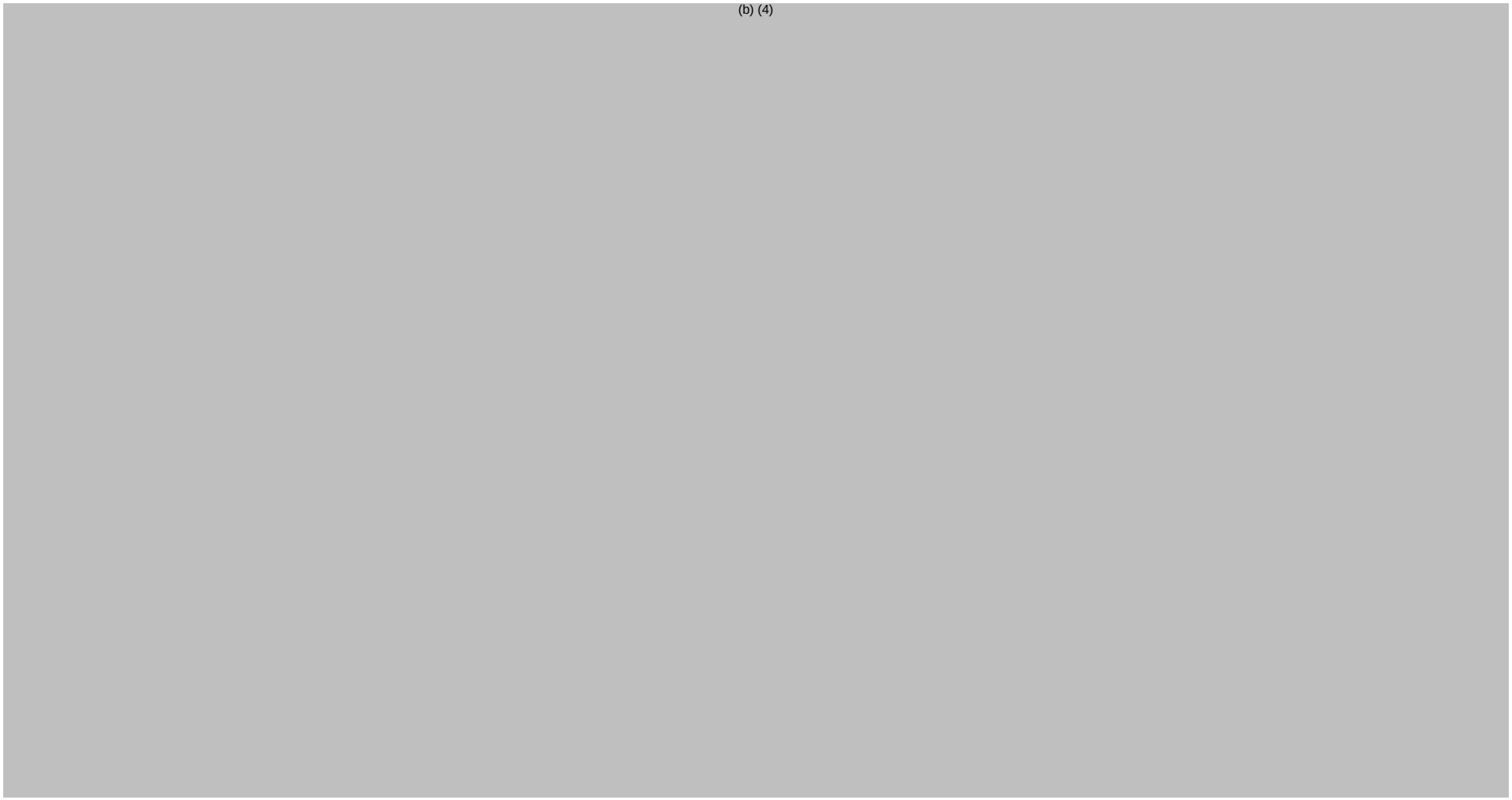

FDA_1303


(b) (4)

Appendix D Pharmacy Survey Protocol Track Change Document: Comparison of 12-month Survey to 24-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Archimedes Pharma US Inc.** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Endo Pharmaceuticals Inc.** **Galena Biopharma** **Insys Therapeutics** **Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**5~~4~~.0**
DATE:	**10 Sep~~22 May~~ 2013**
APPROVED:	**FINAL**

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LIST OF APPENDICES

FDA_1307

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CSP	Closed System Pharmacy
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE/PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt; Mylan, Inc.; the Pharmaceuticals Business of Covidien; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between TIRF medicines
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI). This protocol will describe the administration of the surveys that will be conducted among pharmacists who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists around the following key information and risk messages communicated through REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of pharmacists who are enrolled in the TIRF REMS Access Program. Respondents who have participated in the first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered via the Internet through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take up to 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the KAB survey results for pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions.

Qualitative research was performed with 7 pharmacists who were recruited from the list of pharmacists who completed surveys for the 12-month TIRF REMS Assessment and met the definition of "low performer", i.e., provided an incorrect response on 3 to 5 of the 7 targeted responses/questions from the 12-month TIRF REMS Assessment.

Among the pharmacists interviewed, the most notable finding was that their survey responses should be based on ("according to") the TIRF medicines label. The findings from this research have been incorporated into the survey in Appendix A. The qualitative research report can be found in Appendix C.

4.1.2 Questions and Statements on REMS Goals

The Knowledge, Attitudes, and Behaviors (KAB) questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);
- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- One question allowing for the respondent to list questions or comments.

FDA_1311

Questionnaires will be analyzed to determine pharmacist understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

FDA_1312

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

FDA_1313

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
80	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors. The following question about behaviors will be asked after the key risk message questions.

Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

FDA_1315

4.2 Participant Recruitment

A random sample of "pharmacists in charge" from pharmacies that are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. Any pharmacist who works at an enrolled pharmacy may participate. The text of the sample written invitation to pharmacists can be found in Appendix B.

If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-respondents from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of pharmacists will be randomly selected. The unique code provided in the invitation letter will be linked to the type of pharmacy (inpatient, outpatient, or Closed System Pharmacy [CSP]) in which the pharmacist works, based on the information provided as part of the TIRF REMS Access Program enrollment.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium to thank them for their participation. The mailing will include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating pharmacists will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of pharmacies (e.g., chain and independent store) for participation.

Pharmacists will be offered Internet-based or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the Internet-based survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 pharmacists who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate

for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

Pharmacists who work at pharmacies that are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Pharmacists who have previously participated in the TIRF REMS KAB survey.
- Pharmacists or their immediate family members who have ever worked for Anesta LLC, Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~, the Pharmaceuticals business of Covidien~~; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; ProStrakan, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth;or the FDA.

FDA_1317

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm pharmacist eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Pharmacist-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of pharmacists who do not have Internet access or prefer taking the survey over the telephone. It will also be convenient for pharmacists to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the pharmacist selects to participate in the survey via the Internet, he/she will be directed to a secured website where he/she will be instructed to complete screening questions. An Internet-based survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified time period when the Survey Coordinating Center is available.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer interviews.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question

once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to pharmacists
- The number of reminder letters issued to pharmacists
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who answered all questions presented to themcompleted the survey
- Representativeness of pharmacists based on geography
- Description of survey participants, including:
    - Gender
    - Years of professional experience
    - How many times per month TIRF medicines dispensed in the last 6 months

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible pharmacists who completed all questions presented to them in the survey ("completers").

7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

FDA_1319

7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of completersrespondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

7.1.4 Analysis Population

The analysis population will be based on eligible pharmacists who completed the survey.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if they have questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE/PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE/PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $50 honorarium, a Thank You Letter, correct survey responses to key risk message questions, and the ISI after the survey is completed. Respondent contact information is also needed in the event that a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to dispense TIRF medicines.

Appendix A Pharmacist Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

FDA_1321

Survey Legend

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
  West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV

Survey Legend

– Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN ~~ONLINE/PHONE~~ SURVEY CONTENT]

~~[PREAMBLE 1]~~

~~Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." (INTERVIEWER: Say "TIRF" then spell out T-I-R-F) The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~**[ONLINE PREAMBLE 1]**

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; ~~(the Pharmaceuticals Business of Covidien); Meda Pharmaceuticals;~~ and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

~~[ONLINE ONLY]~~How We Use Your Information

~~[PHONE ONLY] Now I would like to read some information about how your contact information will be used.~~

Comment [24mos1]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

~~[ONLINE ONLY]~~ How We Protect Your Privacy

~~[PHONE ONLY]Now I would like to tell you some information about how we protect your privacy.~~

Comment [24mos2]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

~~[ONLINE ONLY]~~ How to Learn More about This Survey

Comment [24mos3]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble

~~[ONLINE ONLY]~~ If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

~~ONLY~~]Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-

3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

~~**[ONLINE ONLY]** Taking the Survey~~

~~**[ONLINE ONLY]** Once you have answered a question and moved on, you cannot go back and change your answers.~~

~~**[ONLINE ONLY]** Thank you for your participation in this survey.~~

[END PHONE PREAMBLE 1]

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[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[ONLY TERMINATE AFTER WAVE 1]**
   - ○ No
   - ○ I don't know **[ONLY TERMINATE AFTER WAVE 1]**

3. Do you work in a pharmacy that is enrolled in the TIRF REMS Access program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Archimedes Pharma US Inc.**[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Endo Pharmaceuticals Inc. **[TERMINATE]**
   - □ Galena Biopharma **[TERMINATE]**

- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~ **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ ProStrakan, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
7a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
7d. Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

[RANDOMIZE LIST]	True	False	I don't know
11a. 8 mg oral hydromorphone/day	○	○	○
11b. 60 mg oral morphine/day	○	○	○
11c. 30 mg oral oxycodone/day	○	○	○
11d. 25 mcg transdermal fentanyl/hour	○	○	○
11e. 25 mg oral oxymorphone/day	○	○	○
11f. An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a. Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b. Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c. Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d. Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e. Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f. Give patients (or their	○	○	○	○	○

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caregivers) the Medication Guide for their TIRF medicine

13. Please answer True, False, or I don't know for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
13a.	TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
13b.	All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.	○	○	○
13c.	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

14. **[INPATIENT PHARMACIST]** Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program?

- ○ Yes
- ○ No
- ○ I don't know

15. **[OUTPATIENT PHARMACIST]** Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system?

- ○ Yes
- ○ No
- ○ I don't know

16. **[CSP OUTPATIENT PHARMACIST]** Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?

- ○ Yes
- ○ No
- ○ I don't know

17. **[INPATIENT PHARMACIST]** Please answer True, False, or I don't know for the following statement about TIRF medicines.

	True	False	I don't know
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	○	○	○

[PREAMBLE 3]

The next set of questions is about the educational materials for TIRF medicines. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

18. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q20]**
- ○ I don't know **[GO TO Q20]**

19. Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

20. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

23. What are your questions? **[MULTILINE INPUT]**

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

24. Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?

- ○ Yes
- ○ No
- ○ I don't know

25. On average, how many times per month have you dispensed TIRF medicine within the last 6 months?

- ○ None **[Go to DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

26. Please select the TIRF medicine(s) that you have dispensed within the last 6 months (select all that apply):

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora® ~~or generic Fentora®~~
- ☐ Lazanda ®
- ☐ Onsolis®
- ☐ Subsys®

[DEMOGRAPHICS PREAMBLE 2]

These last few questions are for demographic purposes.

27. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

28. In total, how many years have you been a practicing pharmacist?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

29. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $50 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name

and address you will not receive the honorarium for your time and participation in the survey.

Do you agree to give us your name and mailing address so we can send you the honorarium?

○ Yes

○ No **[SKIP TO CLOSING 2]**

[END CLOSING 1]

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END CLOSING 3]

[END OF SURVEY CONTENT]

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Appendix B Pharmacist Invitation Letter

[CURR_DATE]

[PHARMACY_NAME]

[PHARMACY _STREET_ADDR]
[PHARMACY_CITY], [PHARMACY _STATE] [PHARMACY _ZIP]

[PHARMACY_FAX_NUMBER]

Dear [PHARMACIST_IN CHARGE]

Your Pharmacy was selected to receive this letter, because of enrollment in the TIRF REMS Access Program. We are contacting you to inform you about a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Meda Pharmaceuticals; Mallinckrodt; Mylan, Inc.; ~~the Pharmaceuticals Business of Covidien;~~ and Par Pharmaceutical, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

You are under no obligation to participate in this survey. Only one pharmacist from each enrolled pharmacy can participate. If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**. ***We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.***

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

Sincerely,

The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

Appendix C Qualitative Research Report

FDA_1341

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 2, 24-month REMS Assessment Version 1.0
Survey Time Period	16 September 2013 to 17 October 2013
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies**: Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics Mallinckrodt Pharmaceuticals Meda Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	18 December 2013

Confidentiality Statement

The information contained herein is confidential and the proprietary property of the TRIG of Companies and its affiliates, and any unauthorized use or disclosure of such information without the prior written authorization of the TRIG is expressly prohibited.

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LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE/PC/PSP	Adverse Event/Product Complaint Project Specific Procedure
ANDA	Abbreviated New Drug Application
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
KAB	Knowledge, Attitudes, and Behavior
NDA	New Drug Application
PPAF	Patient-Prescriber Agreement Form
QR	Qualitative Research
REMS	Risk Evaluation and Mitigation Strategy
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

1. PRESCRIBER SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and their generic equivalents. The TIRF Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG) includes Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics, Meda Pharmaceuticals, Mallinckrodt Pharmaceuticals, Mylan, Inc., and Par Pharmaceutical, Inc. At the time of protocol finalization for the Knowledge, Attitude, and Behavior (KAB) surveys, Depomed, Inc. acquired the New Drug Application (NDA) for Lazanda (29 July 2013) from Archimedes Pharma US, Inc., who is no longer a TIRF Sponsor. In addition, Galena Biopharma acquired the NDA for Abstral from ProStrakan Inc., and is now a TIRF Sponsor (as of 01 May 2013) whereupon ProStrakan exited the group. Additionally, Mylan became a TIRF Sponsor on 29 May 2013 due to a pending Abbreviated New Drug Application (ANDA).

The Food and Drug Administration (FDA) has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on 28 December 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information of each product.

The protocol describes the administration of the surveys conducted among prescribers who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

This report describes the results from the prescriber survey conducted for the 24-month TIRF REMS Access Program Assessment. The 24-month prescriber KAB survey launched on 16 September 2013 and closed on 17 October 2013.

2. PRESCRIBER SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behaviors of prescribers regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq and equivalent generics) who are receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist, and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey also collects data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions that were constructed to test prescriber understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Development: FDA Feedback and Qualitative Research of Draft Survey Questionnaire

On 12 March 2013, FDA provided feedback on the 12-month TIRF REMS Access Program Assessment Report that included recommendations for modification to the prescriber survey, as described below.

(1) Add the questions, identified below, as key risk messages in the 24-month TIRF REMS Access Program Assessment Report and investigate the cause for low scores to these questions specifically relating to the safe use questions that potentially indicate poor understanding of these concepts. *The following questions, identified by the FDA, were moved to key risk messages.*

12-month Survey Question Number	24-month Survey Question Number	Question
5	**5**	Please answer "True," "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:
5a	**5a**	Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer
5b	**5b**	Who are not currently taking opioid therapy, but have taken opioid therapy before
5c	**5c**	Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl
8	**9**	For which of the following indications do you prescriber TIRF medicines to opioid tolerant patients? Please answer "Yes," No," or "I don't know" for each option
8e	**9e**	Chronic non-cancer pain
11	**13**	The following patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Please answer "Yes," "No," or "I don't know" as to whether each patient should receive a TIRF medicine.
12	**14**	A patient is already taking a TIRF medicine but wants to change their medicine. The doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed? For each of the following scenarios, please indicate if it is a correct action for the prescriber by answering "Yes," "No," or "I don't know."

(2) Investigate the cause for low scores to specific key risk message questions specifically relating to the safe use questions outlined below:

12-month Survey Question Number	24-month Survey Question Number	Question
5	**5**	Please answer "True," "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:
5a	**5a**	Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer
5c	**5c**	Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl
8	**9**	For which of the following indications do you prescriber TIRF medicines to opioid tolerant patients? Please answer "Yes," No," or "I don't know" for each option
8e	**9e**	Chronic non-cancer pain
11	**13**	The following patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Please answer "Yes," "No," or "I don't know" as to whether each patient should receive a TIRF medicine
11a	**13a**	Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months
12	**14**	A patient is already taking a TIRF medicine but wants to change their medicine. The doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed? For each of the following scenarios, please indicate if it is a correct action for the prescriber by answering "Yes," "No," or "I don't know."
12c	**14c**	Convert from the other TIRF medicine to the new TIRF medicine at half of the dose
12d	**14d**	The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain

12-month Survey Question Number	24-month Survey Question Number	Question
15	**17**	A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please select "True," "False," or "I don't know" for each of the following statements
15a	**17a**	The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal
15b	**17b**	Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression
15c	**17c**	There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines
15d	**17d**	The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient

(3) Investigate the causes, including conducting a pre-testing of all questions related to all key risk messages prior to the next survey, to determine the reasons for the poor performance on these questions. If pre-testing indicates that a rephrasing of a question is indicated, please also re-test the rephrased question and then submit the results of both the pre-testing and re-testing.

3.1.1 Qualitative Research

Before implementing the 24-month survey, TRIG conducted qualitative research (QR) interviews of 12 items from the Prescriber REMS Assessment Survey Questions and 2 new questions that were not included in the 12-month survey (see Appendix C). The research undertaken in this QR process included:

- Review of the questions identified by the FDA that had a low correct response rate;
- Review of two new questions created to assist in determining the understanding of the term "around-the-clock usage";
- Review of proposed new wording on various questions.

The objectives of this research were to:

- Evaluate clarity and comprehension of questions and answer options used in the 12-month assessment;
- Identify terms, questions or topics for clarification or revision based on any areas of confusion with or misunderstanding for current wording;

- Determine how participants understand specific questions and why those questions are answered a particular way;
- Determine how certain questions might be understood differently and answered more accurately if further clarified;
- Evaluate alternative language for these questions.

This QR involved in-depth, individual telephone interviews with 7 prescribers. Each interview lasted about 45 minutes. All interviews were conducted by the same experienced moderator using a detailed discussion guide that probed into each area of the survey questions identified for further investigation. The strategy used to conduct the 7 telephone interviews was to interview:

- 7 TIRF REMS Access-enrolled prescribers who completed the 12-month Prescriber REMS Assessment Survey and met the definition of a "low performer" based on their incorrect responses to between 3 and 7 of the 10 items identified by FDA.

Based on the outcome of the QR, the questions shown below were added or reworded for Wave 2. A track change version of the protocol can be found in Appendix D.

The following new questions were added to the 24-month REMS Assessment based on QR findings.

24-month Survey Question Number	Question
6	Please answer "True," "False," or "I don't know" for each statement about TIRF medicines
6a	A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time
6b	A cancer patient who has been on an around-the-clock opioid for 1 day can start taking TIRF medicines for breakthrough pain
19	Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine? Y/N/IDK

The following questions were revised for the TIRF REMS KAB 24-month survey:

12-month Survey Question Number	12-month Question	24-month Survey Question Number	24-month Question
5	Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	**5**	Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:
5a	Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer	**5a**	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer
5c	Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	**5c**	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy
11	The following patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Please answer "Yes," "No," or "I don't know" as to whether each patient should receive a TIRF medicine.	**13**	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.
11b	Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks	**13b**	Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

12-month Survey Question Number	12-month Question	24-month Survey Question Number	24-month Question
12	A patient is already taking a TIRF medicine but wants to change their medicine. The doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed? For each of the following scenarios, please indicate if it is a correct action for the prescriber by answering "Yes," "No," or "I don't know."	**14**	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option
12c	Convert from the other TIRF medicine to the new TIRF medicine at half of the dose	**14c**	Convert from the other TIRF medicine to the new TIRF medicine at half of the dose
12d	The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain	**14d**	The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain
15	A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please select "True," "False," or "I don't know" for each of the following statements	**17**	A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.
15a	The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal	**17a**	The patient can't be prescribed erythromycin, because using it at the same time as TIRF medicine could be fatal.
15b	Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression	**17b**	Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
15c	There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines	**17c**	There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.

12-month Survey Question Number	12-month Question	24-month Survey Question Number	24-month Question
15d	The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient	**17d**	The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.
N/A[1]	-Not asked-	**17e**	I don't know

[1] Question not asked in the 12-month Survey

After the initial review and subsequent to QR, the survey was updated and re-submitted to the FDA. The FDA provided feedback and the following revisions were made (see Appendix A and Appendix B) to the survey and protocol, as appropriate, to incorporate these requests:

- Revise the statement on page 11 of the proposed survey protocol of "Participants will be informed that prescribers from these states are not eligible to participate and physicians who practice in these states will not receive compensation for their participation." to "Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation."

This change was made in the protocol and the survey invitation letter.

- Base the study analysis for representativeness of prescribers on at least prescribers' medical specialty, medical degree, and geography.

Representativeness of prescribers' on their medical specialty, medical degree, and geography, the comparison of medical specialty and medical degree were not calculated because this data was not available for analysis.Include in analyses all eligible surveys that are completed.

- Include in analyses all eligible surveys that are completed.

This information was incorporated in the 12-month report; it will also be incorporated in all subsequent analyses

Appendix C includes a copy of the Top-Line Findings Report: Findings Report: Qualitative Research to Evaluate the Prescriber and Pharmacist 12-month REMS Assessment Surveys for TIRF Medicines.

3.2 Survey Sample

This survey was conducted among a random sample of prescribers who were enrolled in the TIRF REMS Access Program as of 15 August 2013. A target sample of 300 prescribers who

were enrolled in the TIRF REMS Access Program was planned for the survey. The size of the sample was determined based on both practical and statistical considerations.

3.2.1 Eligibility

Subject recruitment was from a random sample of prescribers who were enrolled in the TIRF REMS Access Program. Respondents or their immediate family members who had ever worked for any of the TRIG companies, RelayHealth, McKesson Specialty Care Solutions, United BioSource Corporation (UBC), or the FDA were not eligible to participate.

Respondents who participated in the first wave of the TIRF survey (12-month TIRF REMS Access Program Assessment) were not eligible to participate.

3.2.2 Recruitment

Subject recruitment was performed via a letter sent through the United States Postal Service (USPS), and via email (Section 5.1.1 for more detail).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; thus a second and a third mailing were sent to non-respondents from the original sample to maximize participation. Following the third mailing, the prescriber survey sample had not reached the target; therefore, a new random sample was selected and invitations were mailed through the USPS or e-mailed.

Prescribers were given the option of taking the survey by telephone via the Survey Coordinating Center or online via a secure website. All participating prescribers were offered an honorarium of $125 for a completed survey. The survey was estimated to take approximately 20 minutes to complete.

3.3 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the prescribers' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that use "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages is generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

3.3.1 Key Risk Message 1

Key Risk Message 1 referred to the prescriber's knowledge of the specific contraindications for TIRF medicines in opioid non-tolerant patients. Questions in **bold face type** were added as key risk message questions based on FDA Feedback.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	**Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:**	
5a	**Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer**	***True***
5b	**Who are not currently taking opioid therapy, but have taken opioid therapy before**	***False***
5c	**Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy**	***False***
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***

3.3.2 Key Risk Message 2

Key Risk Message 2 referred to the prescriber's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients. Questions in **bold face type** were added as key risk message questions based on FDA Feedback. This key risk message includes both a behavior question (Question 9) and a knowledge question (Question 13).

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	**Chronic non-cancer pain**	***No***
13	**The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.**	**13b. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.**

3.3.3 Key Risk Message 3

Key Risk Message 3 referred to the prescriber's knowledge of the risk factors and signs and symptoms of opioid abuse in patients who take TIRF medicines.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***

3.3.4 Key Risk Message 4

Key Risk Message 4 referred to the prescriber's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage. Questions in **bold face type** were added as key risk message questions based on FDA Feedback.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***
14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	**14b. The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.**

3.4 Additional Questions

The survey also contained questions (Question 12a-f) about the requirements of the TIRF REMS Access Program and the use of the TIRF educational materials in their practice. The following questions about behaviors were asked after the key risk message questions:

Question No.	Question
12	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."
12a	Ask patients (or their caregivers) about the presence of children in the home
12b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
12c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
12d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
12e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
12f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible prescribers who completed the survey. Eligible prescribers were defined as those respondents who answered ***Yes*** to Question 1 (agree to take part in survey), and Question 3 (enrolled in the TIRF REMS Access program), and ***No*** to Question 2 (participated in past survey) and Question 4 (worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA). A completed survey was a survey from an eligible prescriber in which all non-eligibility questions were answered as appropriate. Note that some questions may not be answered because of skip logic in the survey questionnaire.

4.1.2 Sub-populations of Interest

The following sub-group analyses were conducted if the sub-group included at least 20 respondents.

Sub-group analysis 1: Reading Medication Guide or Full Prescribing Information (Questions 20, 21, 22, and 23):

- S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.
- S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered “No” or “I don’t know” to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered “No” or “I don’t know” to Question 23).

Sub-group analysis 2: Medical degree of respondents (Question 32):

- S-2a - MD
- S-2b - DO
- S-2c - Nurse Practitioner
- S-2d - Physician Assistant

Sub-group analysis 3: Time to complete survey - Internet:

- S-3a - <10 min
- S-3b - 10 to <20 min
- S-3c - ≥ 20 min

Sub-group analysis 4: Time to complete survey - Telephone:

- S-4a - <10 min
- S-4b - 10 to <20 min
- S-4c - ≥ 20 min

Sub-group analysis 5: Modality to complete survey:

- S-5a - Internet
- S-5b – Telephone

Sub-group analysis 6: Time practicing medicine (Question 33):

- S-6a - Less than 3 years
- S-6b - 3 to 5 years
- S-6c - 6 to 15 years
- S-6d - More than 15 years

Sub-group analysis 7: Number of times per months prescribing TIRF medicines within the last 6 months (Question 29):

- S-7a - None
- S-7b - 1-2 times a month
- S-7c - 3 - 5 times a month
- S-7d - More than 5 times a month

Sub-group analyses will be performed for Tables 6.1 and 6.2, 7.1, 7.2, 8.1, 8.2, 9.1, 9.2.

4.1.2.1 Primary Analyses

Primary analyses were performed for all key risk messages, evaluating the number and percentage of correct responses for each individual question/item defined by the key risk message. The correct response to each question/item was identified in the body of the risk message table (Section 3.3).

4.1.2.2 Secondary Analyses

Secondary analyses evaluated the number and percentages of correct responses and the average number of correct answers within the risk message to assess demonstrated understanding of the comprehensive key risk message. A correct response rate of 65% or

greater was considered to represent adequate understanding of each concept or key risk message.

4.1.3 Prescriber Report of Adverse Event, Product Complaint, or Medical Information Request during Survey

A prescriber may have reported a product complaint, or an adverse event experienced by their patients either while taking the online survey in the free text field or while in conversation with the Survey Coordinating Center. If the event was mentioned to a Survey Coordinating Center Associate, the Associate documented the safety event and the respondent's contact information, if provided. The prescriber was also informed that a representative from the appropriate TIRF medicine manufacturer may contact them to obtain additional information about the adverse event or product complaint. Surveys completed on the Internet were monitored for any comments recorded in the free text field. Information on all reports (Internet or Telephone) that constituted an adverse event or product complaint was forwarded to the appropriate TIRF medicine manufacturer for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the prescriber responses to questions in the KAB survey are summarized in this section, and a full set of responses can be found in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 5,108 prescribers were sent letters inviting them to participate in this survey (Table 1). An additional 11,986 reminder letters were sent. Some prescribers may have received more than 1 reminder letter.

In all, 425 prescribers who expressed interest in the survey were screened for eligibility. The number of respondents found eligible for participating in the survey was 302, all of whom completed the survey. Of the 302 eligible complete respondents, 289 (95.7%) completed the survey online, and 13 (4.3%) completed it by telephone (Table 3). There were no duplicate surveys.

Based on the TRIG Sponsors interpretation of state laws regarding prescriber reimbursement, respondents from Massachusetts (MA), Vermont (VT), and Minnesota (MN) were eligible to participate in the survey; however, they were not eligible to receive the $125 honorarium. Letters were sent to prescribers in these states, and 2 respondents from Massachusetts chose to participate despite receiving no honorarium.

Table 1. Survey Participant Administration Results

Summary Statistic	Screened Prescribers N=425[1]	
	All Respondents	
	N	%
Number of invitations issued to prescribers	5108	
Number of reminder letters issued to prescribers	11,986	
Number of prescribers screened for participation	425	
Number of prescribers eligible for participation	302	71.1[1]
Method of Survey Completion		
Number of surveys completed by telephone	13	4.3[2]
Number of surveys completed by internet	289	95.7[2]

[1] The denominator for the percentage of eligible prescribers is the number of screened prescribers (N=425).
[2] The denominator for percentages completed by telephone or Internet is the number of eligible prescribers (N=302).

As shown in Table 2, a total of 425 prescribers agreed to participate in this survey and of those 302 prescribers reported that they were enrolled in the TIRF REMS Access program; 49 (11.5%) prescribers were ineligible because they reported that they were not enrolled in the program or they did not know whether they were enrolled. Seventeen (4.0%) respondents were ineligible because they had previously taken part in the survey about TIRF medicines and 49 (11.5%) respondents did not know if they had participated; therefore, they were considered ineligible. Five respondents were ineligible for the survey because they, or an immediate family member, had worked for UBC or a TRIG company in the past, or did not know whether they, or an immediate family member, had worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or the FDA in the past, and 1 prescriber preferred not to answer and thus was considered ineligible.

Table 2. Survey Participant Screening Results

Question	Screened Prescribers N=425		Eligible Completed Prescribers N=302	
	n	%	n	%
Question 1: Do you agree to participate in this survey?				
Yes	423	99.5	302	100.0
No[1]	2	0.5		
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.				
Yes[1]	17	4.0		
No	357	84.0	302	100.0
I don't know[1]	49	11.5		
Question not asked[2]	2	0.5		
Question 3: Are you enrolled in the TIRF REMS Access program?				
Yes	308	72.5	302	100.0
No[1]	24	5.6		
I don't know[1]	25	5.9		
Question not asked[2]	68	16.0		
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]				
Anesta LLC.[1]	0	0.0		
Archimedes Pharma US, Inc.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	1	0.2		
Endo Pharmaceuticals, Inc.[1]	0	0.0		
Galena Biopharma[1]	0	0.0		
Insys Therapeutics[1]	0	0.0		
Mallinckrodt[1]	0	0.0		
McKesson Specialty Care Solutions[1]	0	0.0		
Meda Pharmaceuticals[1]	0	0.0		
Mylan Inc.[1]	1	0.2		

Table 2. Survey Participant Screening Results

Question	Screened Prescribers N=425		Eligible Completed Prescribers N=302	
	n	%	n	%
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
RelayHealth[1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	2	0.5		
United BioSource Corporation[1]	0	0.0		
FDA[1]	0	0.0		
None of these apply[4]	302	71.1	302	100.0
I don't know[1]	1	0.2		
Prefer not to answer[1]	1	0.2		
Question not asked[2]	117	27.5		

[1] Ineligible to participate in the survey.
[2] Question not asked due to previous question elimination.
[3] More than 1 response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Those taking the survey online took a mean of 17.0 ± 9.75 minutes to complete, while those taking it by telephone took a mean of 27.0 ± 3.16 minutes. Most (n=214; 70.9%) online participants completed the survey within 20 minutes, while all telephone participants (n=75; 24.8%) took 20 minutes or more (Table 3).

Table 3. Time to Complete Survey for Completers Only (Minutes)

Time to Complete Survey			
Summary Statistic	**Telephone**	**Internet**	**Total[1]**
N	13	289	302
Mean (Standard Deviation)	27.0 (3.16)	17.0 (9.75)	17.5 (9.77)
Minimum	21	5	5
Median	26.3	15.0	15.2
Maximum	34	109	109

Table 3. Time to Complete Survey for Completers Only (Minutes)

Time to Complete Survey			
Summary Statistic	**Telephone**	**Internet**	**Total[1]**
Category			
5 – <10 Minutes	0	47	47
10 – <15 Minutes	0	97	97
15 – <20 Minutes	0	70	70
20 – <25 Minutes	3	36	39
25 – <30 Minutes	9	22	31
30 Minutes or More	1	17	18

[1] Number of eligible prescribers completing the survey (See Table 1).

5.1.2 Demographic Characteristics of Prescribers who Completed the Survey

The demographic characteristics of eligible prescribers who completed the survey are presented in Table 4.

The survey included 27.5% respondents from the Northeast, 15.2% from the Midwest, 33.1% from the South, and 23.5% from the West region of the United States (US). The proportion of eligible completed prescribers within each geographic region was similar to the overall proportion of prescribers enrolled in the TIRF REMS Access Program as of 19 October 2013 in each geographic region (Table 4). There were no respondents from Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam identified as "Other" in Table 4.

The most common healthcare degree was an MD (60.3%), and the most common medical specialties were pain management (49.0%) and oncology (22.8%). Of respondents who were medical doctors, 117 of the respondents (38.7%) had practiced medicine for more than 15 years.

Table 4 Demographic Characteristics of Eligible Prescribers

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 31: What is your gender?		
Male	197	65.2
Female	103	34.1
Prefer not to answer	2	0.7
Question 32: What is your medical degree?		
MD	182	60.3
DO	22	7.3
Nurse Practitioner	66	21.9
Physician's Assistant	30	9.9
Prefer not to answer	2	0.7
Question 33: In total, how many years have you been practicing medicine, since completing your post-graduate education?		
Less than 3 years	28	9.3
3-5 years	49	16.2
6-10 years	55	18.2
11-15 years	51	16.9
More than 15 years	117	38.7
Prefer not to answer	2	0.7
Question 35: What is your medical specialty?		
Oncology	69	22.8
Primary Care	30	9.9
Pain Management	148	49.0
Other (please specify)[2]	53	17.5

Table 4 Demographic Characteristics of Eligible Prescribers

Question	Eligible Completed Prescribers N=302[1]			
	n		%	
Question 34: In which state or US Territory do you practice?[3]				
Geographic Region[3]	**Eligible and Complete Respondents N=302**		**Enrolled in TIRF REMS Access Program as of 19Oct2013 N=9042**	
	N	**%**	**N**	**%**
Northeast	83	27.5	2063	22.8
Midwest	46	15.2	1534	17.0
South	100	33.1	3010	33.3
West	71	23.5	2432	26.9
Other	0	0.0	3	0.0
Prefer not to answer	2	0.7		

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] Other medical specialties are presented in Appendix B, Listing 3.

[3] According to the 2001 Geographic Area Regions set by the US Census Bureau, Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico. Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

Verbatim responses of prescribers who described their medical specialty as 'other' (see Table 4) are listed in Appendix B, Listing 2.

5.1.3 Prescribing Habits of Eligible Prescribers Related to TIRF Products

Over the 6 months preceding the survey, 173 (57.3%) of the prescribers recalled prescribing TIRF medicines 1 to 2 times a month. The most frequently prescribed TIRF product was Actiq or its generic equivalent (74.2% of prescribers), followed by Fentora by 58.5% of prescribers Table 5.

Table 5. Prescribing Habits of Respondents Completing the Survey

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 29: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?		
None	54	17.9
1-2 times per month	173	57.3
3-5 times per month	44	14.6
More than 5 times per month	18	6.0
I don't remember	13	4.3
Question 30: Please select the TIRF medicines that you have prescribed within the last 6 months (select all that apply):[2]		
Abstral®	10	4.0
Actiq® or generic Actiq	184	74.2
Fentora®	145	58.5
Lazanda®	16	6.5
Onsolis®	4	1.6
Subsys®	56	22.6
N/A (answered ***None*** to Question 29)	54	

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

N/A = Not applicable

5.1.4 TIRF Medicines Educational Materials

Prescribers were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information, the Medication Guide, and the Patient-Prescriber Agreement Form (PPAF) (Table 6). Almost all prescribers reported they had received or had access to the Full Prescribing Information and the Medication Guide (282; 93.4%; 273; 90.4% respectively). Of those with access to these materials, 86.2% and 90.1% indicated that they had read the Full Prescribing Information and the Medication Guide, respectively. Additionally, most prescribers reported reviewing the PPAF with each patient or their caregiver (86.8%); signing the PPAF and having the patient/caregiver sign the PPAF (92.4%); and giving a copy of the PPAF to the patient (80.5%).

Table 6. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form

Question	Eligible Completed Prescribers N=302[1]	
	N	%
Question 20: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine that you prescribe?		
Yes	282	93.4
No	6	2.0
I don't know	14	4.6
Question 21: Did you read the Full Prescribing Information for the TIRF medicine that you prescribe?[2]		
Yes	243	86.2
No	33	11.7
I don't know	6	2.1
N/A (answered ***No*** or ***I don't know*** to Question 20)	20	
Question 22: Did you receive or do you have access to the Medication Guide for the TIRF medicine that you prescribe?		
Yes	273	90.4
No	8	2.6
I don't know	21	7.0
Question 23: Did you read the Medication Guide for the TIRF medicine that you prescribe?[2]		
Yes	246	90.1
No	24	8.8
I don't know	3	1.1
N/A (answered ***No*** or ***I don't know*** to Question 22)	29	
Question 24: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[3]	37	12.3
No	243	80.5
I don't know	22	7.3

Table 6. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form

Question 26: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?		
Yes	262	86.8
No	25	8.3
I don't know	15	5.0
Question 27: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?[2]		
Yes	242	92.4
No	12	4.6
I don't know	8	3.1
N/A (answered ***No*** or ***I don't know*** to Question 26)	40	
Question 28: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?		
Yes	243	80.5
No	34	11.3
I don't know	25	8.3

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question and this may not reflect the entire sample because of skip logic in the survey.

[3] Verbatim texts for questions about the information in the Full Prescribing Information are presented in Appendix B, Listing 1.

There were 37 (12.3%) respondents who typed a response into the free text field for Question 24 (*Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?*). The verbatim responses are listed in Appendix B, Listing 1).

5.2 KAB Survey Objectives

5.2.1 Key Risk Message Results

The focus of this section of the document is on the findings for the total eligible respondent population who completed the survey. A summary of results by sub-group are described in a separate section of the document, Section 5.2.3.

5.2.1.1 Key Risk Message 1

Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients.

Analysis of responses to components of Question 5 for Key Risk Message 1 showed that a high percentage of prescribers understand that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur (n=265; 87.7%) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (n=283; 93.7%). Most prescribers were aware patients just starting a TIRF medicine must begin with titration from the lowest available dose for that product (n=244; 80.8%) and that TIRF medicines may not be used to treat opioid non-tolerant patients (n=242; 80.1%), (Table 7). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 6.0 out of 7.

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=302[1]	
	N	% (95% CI)[3]
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer[5]		
True[2]	273	90.4 (86.5, 93.5)
False	24	7.9
I don't know	5	1.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	28	9.3
False[2]	266	88.1 (83.9, 91.5)
I don't know	8	2.6

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=302[1]	
	N	% (95% CI)[3]
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	39	12.9
False[2]	248	82.1 (77.3, 86.3)
I don't know	15	5.0
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	265	87.7 (83.5, 91.2)
False	32	10.6
I don't know	5	1.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	283	93.7 (90.3, 96.2)
False	3	1.0
I don't know	16	5.3
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		
True	43	14.2
False[2]	242	80.1 (75.2, 84.5)
I don't know	17	5.6

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible Completed Prescribers N=302[1]	
	N	% (95% CI)[3]
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	244	80.8 (75.9, 85.1)
False	52	17.2
I don't know	6	2.0
Secondary Analysis: Demonstrated Understanding		
0 correct responses	1	0.3
1 correct response	2	0.7
2 correct responses	1	0.3
3 correct responses	7	2.3
4 correct responses	23	7.6
5 correct responses	41	13.6
6 correct responses	90	29.8
7 correct responses	137	45.4
Average number of correct responses[4]	6.0	(5.8, 7.0)

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals. One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

[5] Question 5a was included in the protocol as follows: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer. The word "chronic" was replaced with "cancer" and presented to the prescribers in the survey accurately.

5.2.1.2 Key Risk Message 2

Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (*16 Years of Age and Older for Actiq Brand and Generic Equivalents*) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain.

Responses to components of Question 9 for Key Risk Message 2 indicate that a high percentage of respondents prescribe TIRF medicines for the approved indication of treatment of breakthrough cancer pain in opioid-tolerant patients (n=279; 92.4%) and not for patients with acute or postoperative pain (5.6%), headache or migraine pain (6.6%), or dental pain (1.7%) (Table 8). Question 13 presented respondents with descriptions of 4 patients experiencing breakthrough pain and asked them to select the case that should not receive a TIRF medicine. The correct response was given by 199 (65.9%) prescribers. Because Question 9 is related to the behavior of the prescribers, the secondary analysis showing demonstration of understanding could not be performed.

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.		
9a: Acute or postoperative pain		
Yes	17	5.6
No[4]	281	93.0 (89.6, 95.6)
I don't know	4	1.3
9b: Headache or migraine pain		
Yes	20	6.6
No[4]	279	92.4 (88.8, 95.1)
I don't know	3	1.0
9c: Dental pain		
Yes	5	1.7
No[4]	292	96.7 (94.0, 98.4)
I don't know	5	1.7

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
9d: Breakthrough pain from cancer		
Yes[4]	279	92.4 (88.8, 95.1)
No	22	7.3
I don't know	1	0.3
9e: Chronic non-cancer pain		
Yes	119	39.4
No[4]	178	58.9 (53.2, 64.5)
I don't know	5	1.7
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
13a: Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	36	11.9
13b: Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	199	65.9
13c: Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	12	4.0

Table 8. Responses Linked to Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
13d: Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	28	9.3
13e: I don't know	27	8.9

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] Indicates the desired behavior(s) to each question or item within the question.

5.2.1.3 Key Risk Message 3

Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Responses to components of Questions 7, 8, and 10 for Key Risk Message 3 showed that a high percentage of prescribers were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines (99.0%), a personal history of psychiatric illness is a risk factor for opioid abuse (82.8%), a personal history of past or current alcohol or drug abuse or family history of drug and alcohol abuse is a risk factor for opioid abuse (99.0%), and that TIRF medicines can be abused in a manner similar to other opioid agonists (96.4%). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.8 out of 4 (Table 9).

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
Question 7: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	299	99.0 (97.1, 99.8)
False	2	0.7
I don't know	1	0.3
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	250	82.8 (78.0, 86.9)
No	31	10.3
I don't know	21	7.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	299	99.0 (97.1, 99.8)
No	2	0.7
I don't know	1	0.3
Question 10: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	291	96.4 (93.6, 98.2)
False	9	3.0
I don't know	2	0.7

Table 9. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics.

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)[3]
Secondary Analysis: Demonstrated Understanding		
0 correct responses	0	0.0
1 correct response	0	0.0
2 correct responses	8	2.6
3 correct responses	53	17.5
4 correct responses	241	79.8
Average number of correct responses [4]	3.8	(3.6, 4.0)

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] All confidence intervals are exact binomial 95% confidence intervals.

[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.1.4 Key Risk Message 4

Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration.

Responses to components of Questions 10 and 14 for Key Risk Message 4 showed that 279 (92.4%) prescribers understood that TIRF medicines are not interchangeable with each other regardless of the route of administration, that the conversion of one TIRF medicine to another may result in a fatal overdose (n=286; 94.7%), and that dosing of different TIRF medicines is not equivalent on a microgram-to-microgram basis (n=274; 90.7%). Question 14 dealt with the process the prescribers must adopt in converting a patient from one TIRF medicine to another. In response, 225 (74.5%) prescribers correctly responded that conversion must not be done on a microgram-to-microgram basis (Table 10). Overall, evidence of understanding of the comprehensive key risk message is further supported by the average number of correct responses identified as 3.5 out of 4.

Table 10. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration.

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement about TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	16	5.3
False[2,3]	279	92.4 (88.8, 95.1)
I don't know	7	2.3
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2,3]	286	94.7 (91.5, 96.9)
False	7	2.3
I don't know	9	3.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2,3]	274	90.7 (86.9, 93.8)
False	16	5.3
I don't know	12	4.0
14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
14a: The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	6	2.0
14b: The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	225	74.5 (69.2, 79.3)

Table 10. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration.

Question	Eligible Completed Prescribers N=302[1]	
	n	% (95% CI)
14c: Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25	8.3
14d: The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	34	11.3
14e: I don't know.	12	4.0
Secondary Analysis: Demonstrated Understanding		
0 correct responses	1	0.3
1 correct response	3	1.0
2 correct responses	28	9.3
3 correct responses	75	24.8
4 correct responses	195	64.6
Average number of correct responses[4]	3.5	(3.3, 4.0)

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or item within a question.
[3] All confidence intervals are exact binomial 95% confidence intervals.
[4] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

5.2.2 Other Survey Questions

5.2.2.1 Additional Questions about TIRF Medicines Safety

Table 11 summarizes the prescribers' responses to questions about the safety of TIRF medicines; 21 of these questions were included within key risk message questions (Section 5.2.1) and 17 were additional questions beyond those associated with the key risk messages. Although, Table 11 presents the results of all 38 questions, this section highlights results of responses from the 17 additional questions.

Over half of the (n=183; 60.6%) prescribers surveyed correctly identified that a cancer patient should not be started on a TIRF medicines and an around-the-clock opioid at the same time, while 105 (34.8%) prescribers responded that this is acceptable; 196 (64.9%) of prescribers correctly indicated that a cancer patient who has been on an around-the-clock

opioid for one day should not start taking a TIRF medicine for breakthrough pain; and 160 (53.0%) responded that patients should not continue to take TIRF medicines if they stop taking their around-the-clock opioid medicine. This concept was a key risk message in the patient survey and also resulted in a low score. Prescribers are educated on this concept in the educational program and in the PPAF. Prescribers low understanding of this concept is likely have affected the level of understanding in the patient/caregivers. A majority of prescribers correctly identified the description of opioid-tolerant patients by the listed opioid preparations and corresponding doses of 8 mg oral hydromorphone/day (68.5%), 60 mg oral morphine/day (89.1%), 30 mg/day oral oxycodone (76.2%), 25 mcg transdermal fentanyl/hour (80.8%), 25 mg/day oral oxymorphone (69.9%), or an equianalgesic dose of another oral opioid (65.9%).

Most of prescribers (n=254; 84.1%) correctly indicated that for a patient starting titration with a TIRF medicine, an appropriate dose is the lowest available dose, unless the Full Prescribing Information provides specific guidance (84.1%%). When presented with the scenario of a patient who has started on the lowest dose of a TIRF medicine, and, after 30 minutes, the breakthrough pain has not been sufficiently relieved, 205 (67.9%) prescribers correctly responded that guidance regarding additional doses should be based on the product-specific Medication Guide because the recommendations are not the same for all TIRF medicines.

Question 17 as outlined in Table 11, demonstrates that the majority (225, 74.5%) of prescribers have a high level of understanding pertaining to the safe use of a TIRF medicine with a CYP3A4 inhibitor and the need for monitoring the dosage for their patient. Further, this data reflects that the prescribers clearly understand the need to carefully monitor the patient for opioid toxicity to avoid any potential cause for fatal respiratory depression.

Of the 302 respondents who completed the survey, 199 (65.9%) correctly stated that a patient who had a mastectomy and reconstructive surgery for localized breast cancer with persistent cancer pain managed with 30 mg/day oral morphine for 6 weeks should not receive TIRF medicines because the patient does not meet the definition of opioid tolerant. Furthermore, the majority (225, 74.5%) of prescribers correctly indicated that the prescriber must not convert a patient to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

Nearly all prescribers surveyed (n=298; 98.7%) understood that TIRF medicines contain fentanyl in an amount that could be fatal for children of all ages, for individuals for whom they were not prescribed, and for those who are not opioid tolerant. Two hundred and seventy-eight (92.1%) prescribers were aware that patients must be informed that TIRF medicines should not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain. One hundred and seventy-five (57.9%) prescribers understood that patients should be instructed not to continue their TIRF medicines if they stop taking their around-the-clock opioid medicine; 299 (99.0%) agreed that patients must be instructed not to share their TIRF medicine with anyone else, even if

that person has the same symptoms; and 160 (53.0%) indicated that if patients stop taking their around-the-clock opioid pain medicine, they must stop taking their TIRF medicine.

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 5: Please answer "True," "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:		
5a: Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer.[3]		
True[2]	273	90.4
False	24	7.9
I don't know	5	1.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before.		
True	28	9.3
False[2]	266	88.1
I don't know	8	2.6
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	39	12.9
False[2]	248	82.1
I don't know	15	5.0
Question 6: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
6a: A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.		
True	105	34.8
False[2]	183	60.6
I don't know	14	4.6

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
6b: A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
True	86	28.5
False[2]	196	64.9
I don't know	20	6.6
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	265	87.7
False	32	10.6
I don't know	5	1.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	283	93.7
False	3	1.0
I don't know	16	5.3
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		
False[2]	242	80.1
True	43	14.2
I don't know	17	5.6
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	244	80.8
False	52	17.2
I don't know	6	2.0

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	299	99.0
False	2	0.7
I don't know	1	0.3
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	250	82.8
No	31	10.3
I don't know	21	7.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	299	99.0
No	2	0.7
I don't know	1	0.3
8c: A family history of asthma		
Yes	12	4.0
No[2]	271	89.7
I don't know	19	6.3
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.		
9a: Acute or postoperative pain		
Yes	17	5.6
No[4]	281	93.0
I don't know	4	1.3

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
9b: Headache or migraine pain		
Yes	20	6.6
No[4]	279	92.4
I don't know	3	1.0
9c: Dental pain		
Yes	5	1.7
No[4]	292	96.7
I don't know	5	1.7
9d: Breakthrough pain from cancer		
Yes[4]	279	92.4
No	22	7.3
I don't know	1	0.3
9e: Chronic non-cancer pain		
Yes	119	39.4
No[4]	178	58.9
I don't know	5	1.7
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	291	96.4
False	9	3.0
I don't know	2	0.7
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	16	5.3
False[2]	279	92.4
I don't know	7	2.3

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	286	94.7
False	7	2.3
I don't know	9	3.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	274	90.7
False	16	5.3
I don't know	12	4.0
Question 11: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[2]	207	68.5
False	64	21.2
I don't know	31	10.3
11b: 60 mg oral morphine/day.		
True[2]	269	89.1
False	16	5.3
I don't know	17	5.6
11c: 30 mg oral oxycodone/day		
True[2]	230	76.2
False	47	15.6
I don't know	25	8.3

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
11d: 25 mcg transdermal fentanyl/hour		
True[2]	244	80.8
False	34	11.3
I don't know	24	7.9
11e: 25 mg oral oxymorphone/day		
True[2]	211	69.9
False	39	12.9
I don't know	52	17.2
11f: An equianalgesic dose of another oral opioid		
True[2]	199	65.9
False	68	22.5
I don't know	35	11.6
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	199	65.9
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	36	11.9
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis	12	4.0
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks	28	9.3
I don't know	27	8.9

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
14a. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	6	2.0
14b. The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	225	74.5
14c. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25	8.3
14d. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	34	11.3
14e. I don't know.	12	4.0
Question 15: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.		
The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.[2]	254	84.1
An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	37	12.3
The dose that the prescriber believes is appropriate based on their clinical experience.	8	2.6
The median available dose.	1	0.3
I don't know.	2	0.7

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 16: A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.		
16a. Take another (identical) dose of the TIRF medicine immediately.	73	24.2
16b. Take a dose of an alternative rescue medicine.	16	5.3
16c. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines. [2]	205	67.9
16d. Double the dose and take immediately.	3	1.0
16e. I don't know.	5	1.7
Question 17: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.		
17a: The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	11	3.6
17b: Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.[2]	225	74.5
17c: There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	3	1.0
17d: The dose of the TIRF medicine must be reduced by one-half if a CYP3A4 inhibitor is prescribed in the same patient.	13	4.3
17e: I don't know.	50	16.6

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 18: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select "True," "False," or "I don't know" for each of the following counseling statements.		
18a: TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.		
True[2]	298	98.7
False	1	0.3
I don't know	3	1.0
18b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.		
True[2]	278	92.1
False	16	5.3
I don't know	8	2.6
18c: Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.		
True	95	31.5
False[2]	175	57.9
I don't know	32	10.6
18d: Instruct patients never to share their TIRF medicine with anyone else, even if that person has the same symptoms.		
True[2]	299	99.0
False	3	1.0
I don't know	0	0.0

Table 11. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 19: Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?		
Yes	105	34.8
No[2]	160	53.0
I don't know.	37	12.3

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or item within a question.

[3] Question 5a was included in the protocol as follows: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer. The word "cancer" was replaced with chronic and presented to the prescribers in the survey accurately. The question as presented in the survey has been updated for reporting purposes.

[4]Indicates the desired behavior(s) to each question or item within a question.

5.2.2.2 Prescriber Activities When Prescribing TIRF Medicines

Prescribers were asked about specific activities performed when prescribing TIRF medicines (Table 12).

More than one-half of prescribers (56.3%) indicated they always ask patients (or their caregivers) about the presence of children in the home. Prescribers take care to instruct patients (or their caregivers) not to share TIRF medicines (n=239; 79.1%). When asked about counseling patients/caregivers that accidental exposure to TIRF medicines by a child might be fatal, 197 (65.2%) prescribers selected "always", 63 (20.9%) responded "only with first prescription", and 31 (10.3%) answered "sometimes". In response to the question about instructing patients/caregivers to keep TIRF medicines out of the reach of children, 220 (72.8%) selected "always," 46 (15.2%) selected "only with the first prescription," and 28 (9.3%) selected "sometimes." With regard to instructing patients/caregivers about proper disposal of any unused or partially used TIRF medicines, 187 (61.9%) answered "always," 62 (20.5%) answered "only with the first prescription," and 37 (12.3%) responded "sometimes."

Less than one-half of prescribers (47.0%) always give patients/caregivers the Medication Guide for their TIRF medicine, and 35.8% give their patients/caregivers the Medication Guide for their TIRF medicine only with the first prescription.

Table 12. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."		
12a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	170	56.3
Only with the first prescription	70	23.2
Sometimes	48	15.9
Never	11	3.6
I don't know	3	1.0
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	239	79.1
Only with the first prescription	37	12.3
Sometimes	19	6.3
Never	5	1.7
I don't know	2	0.7
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	197	65.2
Only with the first prescription	63	20.9
Sometimes	31	10.3
Never	8	2.6
I don't know	3	1.0

Table 12. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible Completed Prescribers N=302[1]	
	n	%
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	220	72.8
Only with the first prescription	46	15.2
Sometimes	28	9.3
Never	5	1.7
I don't know	3	1.0
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	187	61.9
Only with the first prescription	62	20.5
Sometimes	37	12.3
Never	12	4.0
I don't know	4	1.3
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	142	47.0
Only with the first prescription	108	35.8
Sometimes	26	8.6
Never	20	6.6
I don't know	6	2.0

[1] Number of eligible prescribers completing the survey (See Table 1).

5.2.3 Analyses of Sub-populations

To assess prescriber understanding of key risk messages, sub-group analyses as described in Section 4.1.2 were conducted. The full set of sub-group analysis tables is provided in Appendix B. With only 13 respondents who completed the telephone survey, sub-group analysis based on time to complete survey using the telephone modality was not carried out. Of the 13 respondents who completed the survey via telephone, the correct response rate when asked to identify patients with cancer who are considered opioid-tolerant was 53.8% by

selecting the "False" response to Question 5b: "*Who are not currently taking opioid therapy, but have taken opioid therapy before*" compared with the correct response rate of 89.6% for those who used the Internet. Of the 13 phone respondents, 7 (53.8%) telephone respondents correctly selected the "False" response for Question 5c: "*Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy"* (Key Risk Message 1) compared with 83.4% in the sub-group that used the Internet (Appendix B, Table 6.1.5).

Of the 35 prescribers who had not read the Medication Guide or Full Prescribing Information, 24 (68.6%) were aware that TIRF medicines may not be used in opioid non-tolerant patients (Question 7c; Key Risk Message 1) compared with 218 (81.6%) prescribers who read the Medication Guide or PI (Appendix B, Table 6.1.1).

65.7% (n=23) of 35 respondents who had not read the Medication Guide or the Full Prescribing Information correctly identified "a personal history of psychiatric illness" as a risk factor for opioid abuse (Question 8a, Key Risk Message 1) compared with 85.0% among those who had read the Medication Guide or PI (Appendix B, Table 8.1.1).

Respondents who completed the survey in less than 10 minutes had a low correct response rate of 57.4% when asked about prescribing an alternate TIRF medicine that is not a bioequivalent generic version of the branded product (Question 14, Key Risk Message 4) compared with the more than 75% correct response rate among those who took longer to complete the survey (Appendix B, Table 9.1.3).

5.3 Spontaneous Comments or Medical Information Requests

Verbatim comments, questions, and requests for medical information are listed in Appendix B, Listing 3.

- Two statements related to lack of clarity regarding definition of opioid-tolerant;
- Three questions related to requests for more information on drug interactions;
- Seven statements dealt with the need for better understanding of dosage and dose titration guidelines; 4 requests concerned guidelines for conversion;
- There were 3 requests for adverse event information;
- Two requests had to do with equianalgesic data;
- One was a request or update medical information; and
- One request was for a copy of the Medication Guide. (Appendix B, Listing 2).

5.4 Summary of Correct Responses for Key Risk Messages

The 4 key risk messages included in the survey included 22 components detailing these key risk messages. Respondents demonstrated a high level of understanding of the 4 key risk messages, as there was a correct response rate of greater than 70% for 20 components of the key risk message questions. Question 13 that asked prescribers to identify from a drop-down list of case descriptions of patients for whom TIRF medicine is not appropriate had a correct response rate of 65.9%. Twelve of the 22 components elicited correct response rates in

excess of 90% (Table 13). A tabulated summary of the results of the primary analyses of correct responses to questions under each key risk message is shown below (Table 13). Directed by the FDA, Question 9 (*In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients?*), which is a behavior assessment question, was included in Key Risk Message 2. Given this question documents behaviors, there is no correct answer but there are desired responses, which according to the protocol was the selection of the "No" responses for the options "acute or postoperative pain, headache or migraine pain, dental pain, and chronic non-cancer pain" and the "Yes" response for the option "breakthrough pain from cancer" (Table 13). Accordingly, the number of responses and percentages shown against each option of Question 9 in Table 13 represent the numbers of respondents and percentages of respondents reporting the desired behavior for each option.

Table 13. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	%
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients	5	Patients with cancer who are considered opioid-tolerant are those:		
	5a	Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer (*Correct Response True*)	**273**	**90.4**
	5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response False*)	**266**	**88.1**
	5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response False*)	**248**	**82.1**

Table 13. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	%
Key Risk Message 1 (cont'd)	7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response True*)	**265**	**87.7**
	7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response True*)	**283**	**93.7**
	7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response False*)	**242**	**80.1**
	7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response True*)	**244**	**80.8**
Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain	9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients?		
	9a	Acute or postoperative pain (*Desired Behavior No*)	**281**	**93.0**
	9b	Headache or migraine pain (*Desired Behavior No*)	**279**	**92.4**
	9c	Dental pain (*Desired Behavior No*)	**292**	**96.7**

Table 13. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	%
Key Risk Message 2 (cont'd)	9d	Breakthrough pain from cancer (*Desired Behavior Yes*)	**279**	**92.4**
	9e	Chronic non-cancer pain (*Desired Behavior No*)	**178**	**58.9**
	13	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine?		
		Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks (*Correct Response*)	**199**	**65.9**

Table 13. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	%
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics	7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True)*	**299**	**99.0**
	8	Which of the following are risk factors for opioid abuse?		
	8a	A personal history of psychiatric illness (*Correct Response Yes*)	**250**	**82.8**
	8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response Yes*)	**299**	**99.0**
	10a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response True*)	**291**	**96.4**
Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration	10b	TIRF medicines are interchangeable with each other regardless of route of administration (*Correct Response False*)	**279**	**92.4**
	10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response True*)	**286**	**94.7**

Table 13. Summary of Correct Responses for Key Risk Messages

Key Risk Message	Question #	Question	Correct Responses	
			N	%
Key Risk Message 4 (cont'd)	10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response True*)	**274**	**90.7**
	14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed?		
	14b	The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose (*Correct Response*).	**225**	**74.5**

6. DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

The prescriber KAB survey included responses from 302 TIRF medicine prescribers invited from a random sample of all prescribers enrolled in the REMS. The specific goals of the prescriber KAB survey was to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed.

Following the 12 March 2013 FDA feedback on the 12-month TIRF REMS Access Program Assessment Report, the survey questionnaire was modified as described in Section 3.1. Based on the FDA recommendations, the key risk message questions listed in Table 14 were reworded and/or added to key risk messages for the 24-month KAB survey. (Questions 5b, 9e, and 13b that were not part of any key risk message in the 12-month survey were added to key risk messages in the 24-month survey.)

As demonstrated in Table 14 there were no significant differences in correct response rates for most questions in each of the key risk messages between the 12-month and 24-month assessments. The 2 questions that elicited noticeably higher rates of correct responses in the 24-month survey were added as key risk message questions for the 24-month survey. These Questions (5a and 5c) related to the concept of opioid-tolerant patients. Although Question 9, identified as a behavior question, was included as a key risk message following the FDA recommendation, the desired response to the item 9e under Question 9 did not show improvement in the present survey over the 12-month survey (Table 14). The inclusion of Questions 5a, and 5c as key risk messages and the re-wording (Section 3.1.1) helped improve the measurement of prescriber understanding. As for the other questions listed in Table 14, the correct response rates were similar for both 12-month and 24-month surveys.

Table 14 Correct Response Rates in the 24-month KAB Survey Compared with the 12-month KAB Survey in Key Risk Message Questions Modified Between the Two Versions

12-Month Survey Question Number	24-Month Survey Question Number	Questions as Presented in the 24-Month Survey	12-Month Survey Correct Response Rate (%)	24-Month Survey Correct Response Rate (%)
5	**5**	Please answer "True," "False," or "I don't know" for each of the following. According to the labeling, patients considered opioid-tolerant are those:		
5a	**5a**	Who are taking regular opioid therapy for underlying persistent cancer pain for one week or longer ***(Correct Response True)***	7.9	90.4
5b	**5b**	Who are not currently taking opioid therapy, but have taken opioid therapy before ***(Correct Response False)***	88.7	88.1
5c	**5c**	Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl ***(Correct Response False)***	15.6	82.1

Table 14 Correct Response Rates in the 24-month KAB Survey Compared with the 12-month KAB Survey in Key Risk Message Questions Modified Between the Two Versions

12-Month Survey Question Number	24-Month Survey Question Number	Questions as Presented in the 24-Month Survey	12-Month Survey Correct Response Rate (%)	24-Month Survey Correct Response Rate (%)
8	**9**	For which of the following indications do you prescriber TIRF medicines to opioid tolerant patients? Please answer "Yes," No," or "I don't know" for each option		
8e	**9e**	Chronic non-cancer pain ***(Desired Behavior No)***	54.3	58.9
11	**13**	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
11b	**13b**	Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. ***(Correct Response No)***	54.3	65.9
12	**14**	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		

Table 14 Correct Response Rates in the 24-month KAB Survey Compared with the 12-month KAB Survey in Key Risk Message Questions Modified Between the Two Versions

12-Month Survey Question Number	24-Month Survey Question Number	Questions as Presented in the 24-Month Survey	12-Month Survey Correct Response Rate (%)	24-Month Survey Correct Response Rate (%)
12b	**14b**	The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose ***(Correct Response)***	75.5	74.5

The concept that a patient must discontinue a TIRF medicine when they stop taking their around-the-clock opioid, while not a key risk message for the prescribers, received a low correct response rate. Prescribers are educated on this concept in the educational program and in the PPAF. Prescribers low understanding of this concept is likely to have affected the level of understanding of respondents in the patient survey. The TRIG is exploring options to increase awareness of this important safety message.

The overall higher level of understanding of the remaining items/questions throughout the 4 key risk messages indicates that prescribers are knowledgeable about the safe of TIRF medicines. The consistent high level of prescribers understanding of key risk messages between the 12-month and 24-month surveys indicates that the prescriber education program is meeting the goals of the TIRF REMS with the tools currently in place.

Appendix A Prescriber Survey Protocol

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Archimedes Pharma US Inc.** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Galena Biopharma** **Insys Therapeutics** **Mallinckrodt** **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**5.0**
DATE:	**10 SEP 2013**
APPROVED:	**FINAL**

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LIST OF APPENDICES

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1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE/PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

FDA_1408

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI) of each product. This protocol will describe the administration of the surveys that will be conducted among prescribers who are enrolled in the TIRF REMS Access Program. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers who are enrolled in the TIRF REMS Access Program. Respondents who participate in the first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the KAB survey results for prescribers included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions.

Qualitative research was performed with 7 prescribers who were recruited from the list of prescribers who completed surveys for the 12-month TIRF REMS Assessment and met the definition of "low performer," i.e., provided an incorrect response on 3 to 7 of the 10 targeted responses/questions from the 12-month TIRF REMS Assessment.

Among the prescribers interviewed, the need to provide a "frame-of-reference" for responding was frequent feedback. In addition, some of the findings suggest potential knowledge gap with respect to:

- Definition of opioid tolerance;
- How to convert patients from one TIRF medicine to another TIRF medicine; and
- Content pertaining to CYP3A4 inhibitors.

The findings from this research have been incorporated into the survey in Appendix A. The qualitative research report can be found in Appendix C.

4.1.2 Questions on REMS Goals

The Knowledge, Attitudes and Behaviors (KAB) questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- One question allowing for the respondent to list questions about the products or comments.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

FDA_1412

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question No.	Question	Desired response
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**
13	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	**13b.** Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.

Question No.	Question	Desired response
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	**14b.** The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following question about behaviors will be asked after the key risk message questions:

Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

FDA_1414

4.2 Participant Recruitment

A random sample of prescribers who are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. The text of the sample written invitation to prescribers can be found in Appendix B. If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-respondents from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of prescribers will be randomly selected.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium to thank them for their participation. Prescribers who practice in Vermont, Massachusetts, or Minnesota and complete the survey will not receive compensation. Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation. The mailing will also include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of prescribers who are invited to participate will be a random sample of all enrolled prescribers. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

Prescribers will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 healthcare providers who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the

precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

All prescribers who are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Prescribers who have previously participated in the TIRF REMS KAB survey
- Prescribers or their immediate family members who have ever worked for ever worked for Anesta LLC, Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; ProStrakan Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Prescriber-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of prescribers who do not have Internet access. It will also be convenient for prescribers to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the prescriber selects to participate in the survey online, he/she will be directed to a secured website to complete screening questions. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any time.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer interviews.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to

minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Gender
  - Medical degree of respondent: MD, DO, NP, PA
  - Medical specialty
  - Years of professional experience
  - How many times per month TIRF medicines prescribed in the last 6 months
  - Geographic region of practice

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible prescribers who completed all questions presented to them in the survey ("completers").

7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if there are questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE/PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE/PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 honorarium, a Thank You Letter, the correct responses to key risk messages, and the ISI after the survey is completed. Respondent contact information is also requested when necessary to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions in addition to instances where a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

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Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe TIRF medicines.

FDA_1420

Appendix A Prescriber Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

Survey Legend

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
- West South Central Division - AR, LA, OK, TX

Survey Legend

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal

physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[ONLY TERMINATE AFTER WAVE 1]**
   - ○ No
   - ○ I don't know **[ONLY TERMINATE AFTER WAVE 1]**

3. Are you enrolled in the TIRF REMS Access program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Archimedes Pharma US Inc. **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Endo Pharmaceuticals Inc. **[TERMINATE]**
   - □ Galena Biopharma **[TERMINATE]**

- ☐ Insys Therapeutics **[TERMINATE]**
- ☐ Mallinckrodt **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ ProStrakan, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select "True," "False," or "I don't know" for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	True	False	I don't know
5a.	Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
6a.	A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b.	A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
7a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
7d.	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

	[RANDOMIZE LIST]	True	False	I don't know
11a.	8 mg oral hydromorphone/day	○	○	○
11b.	60 mg oral morphine/day	○	○	○
11c.	30 mg oral oxycodone/day	○	○	○
11d.	25 mcg transdermal fentanyl/hour	○	○	○
11e.	25 mg oral oxymorphone/day	○	○	○
11f.	An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."

	[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a.	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b.	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c.	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d.	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e.	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f.	Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.

[RANDOMIZE LIST]

13a. ○ Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.

13b. ○ Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

13c. ○ Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.

13d. ○ Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

13e. ○ I don't know

14. A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.

[RANDOMIZE LIST]

14a. ○ The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.

14b. ○ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

14c. ○ Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.

14d. ○ The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

14e. ○ I don't know

15. A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.

[RANDOMIZE LIST]

15a. ○ An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.

15b. ○ The dose that the prescriber believes is appropriate based on their clinical experience.

15c. ○ The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.

15d. ○ The median available dose.

15e. ○ I don't know

16. A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

16a. ○ Take another (identical) dose of the TIRF medicine immediately.

16b. ○ Take a dose of an alternative rescue medicine.

16c. ○ Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

16d. ○ Double the dose and take immediately.

16e. ○ I don't know

17. A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

17a. ○ The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.

17b. ○ Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.

17c. ○ There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.

17d. ○ The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

17e. ○ I don't know

18. Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select "True," "False," or "I don't know" for each of the following counseling statements.

	[RANDOMIZE LIST]	True	False	I don't know
18a.	TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	○	○	○
18b.	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	○	○	○
18c.	Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.	○	○	○
18d.	Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

19. Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?

- ○ Yes
- ○ No
- ○ I don't know

[PREAMBLE 2]

The next set of questions is about the educational materials for TIRF medicines and the TIRF Patient-Prescriber Agreement. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and generic versions of any of these brands.

20. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q24]**
- ○ I don't know **[GO TO Q24]**

23. Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

24. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]**
- ○ I don't know **[GO TO Q260]**

25. What are your questions? **[MULTILINE INPUT]**

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26. Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?

- ○ Yes
- ○ No **[GO TO Q28]**
- ○ I don't know **[GO TO Q28]**

27. Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?

- ○ Yes
- ○ No
- ○ I don't know

28. Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

29. On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?

- ○ None **[GO TO DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

30. Please select the TIRF medicines that you have prescribed within the last 6 months (select all that apply):

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Onsolis®
- ☐ Subsys®

[DEMOGRAPHICS PREAMBLE 2] These last few questions are for demographic purposes.

31. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

32. What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner
- ○ Physician Assistant
- ○ Prefer not to answer

33. In total, how many years have you been practicing medicine, since completing your education?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

34. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

35. What is your medical specialty?

- ○ Oncology
- ○ Primary care
- ○ Pain management
- ○ Other (please specify): _____
- ○ No designated specialty

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $125 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey. As a reminder, physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion.

Do you agree to give us your name and mailing address so we can send you the honorarium?

○ Yes

○ No **[SKIP TO CLOSING 2]**

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

36. Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

FDA_1441

Appendix B Prescriber Invitation Letter

[CURR_DATE]

[PRESCRIBER NAME]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [PRESCRIBER NAME]:

You were selected to receive this letter because you have enrolled in the TIRF REMS Access Program. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys™, and generic versions of any of these brands.

The manufacturers of TIRF medicines (collectively referred to as the "TIRF REMS Industry Group") include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc., and Par Pharmaceutical, Inc. These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and if required to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Prescribers who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating, go to **www.XXXXXXXXXX.com** anytime or call **1-877-379-3297,** 8AM to 8PM Eastern Time Monday through Friday. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.

Please have this letter with you at the time you take the survey. Thank you in advance for your help with this important effort.

Sincerely,

TIRF REMS Industry Group

* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

FDA_1442

Appendix C Qualitative Research Report

FDA_1443

Appendix B Prescriber Survey Listings and Sub-group Analysis Tables

Listing 1 VERBATIM RESPONSES TO QUESTION 24 (Questions about the information in the Full Prescribing Information or Medication Guide)

Verbatim Response
Answered incorrectly -- meant to select 'no questions'
dose titration, any specific guiediliness
How can I get a copy of the medication guide so I can better educate my patients?
HOW TO CONVERSION.
How to dose these medications when converting from other opiate short acting rx?
I asked the pharmacist at the time of prescribing.
I had questions regarding dosing, but they were answered by another physician in the office.
I have received guides in the past and have access at my office where I am not at this time. I have asked the representatives questions in the past that I do not presently remember. I do not have any questions at this moment but answered in that I have had questions in the past.
I have used these products for years, I DID have questions when I began initially using these products. I cannot recall particular questions right now.
It has been a long time since I prescribed the TIRF (Lazanda), so I would need to review both guides prior to prescribing it again. Once I have done so, I would not have any other questions.
More safety issues, and conversion issue questions
na
none
none sorry
none
NOT ENOUGH INFO RE TITRATION OF DOSING
opiods in conjunction with subsys safe and effective doses without causing respiratory depression, side effects that can occur other than respiratory depression
Please send me all the information and monthly update about these meds
Questions were answered by drug rep from Fentora. Question was regarding 3rd dose after taking 2nd dose 30 mins after 1st dose was ineffective.
Side effects on nteeth caries
specifics of opioid interaction
Subsys titration kit instructions and what is in the titration kit
the definition of opioid tolerant patient is confusing.

Verbatim Response
the source or data behind the information related to whether the different brand are equianalgesic or not
they were answered by the rep.
What are the available studies to demonstrate equitable dosing between the many TIRF medications?
what are the interactions with other meds in the cyp450 system?
What are the percentages of Cyp3A4 polymorphisms or any other polymorphism which are currently being investigated involving TIRF?
what dose of morphine is required to be considered opioid tolerant? Have questions about the conversion ratio among the medications
what is the optimal way to use Fentora
where do I accesss this info
Will there be indictations for other diagnoses?
would like conversion chart
none
none
none
none

Listing 2 VERBATIM RESPONSES TO QUESTION 35 (OTHER MEDICAL SPECIALTY)

Verbatim Response
hospice
Family Practice
neurology
Physical Medicine and Rehab
NP
hospitalist
Hospice & Palliative Med
Orthopedics
Hospice & Palliative Care
palliative care
Family Practice & Pain Mgmt & Addiction
PM&R
general surgery
Pulmonary/CCM
Palliative Medicine
PM&R/Addictionology
Internal medicine
Rehab / Pain
Rheumatology
supportive oncology
wound care
Family Practice/Primary Care
Primary care and addictionolgy
Anesthesia Pain
psychiatry
Hospice & Palliative Medicine
rehabilitation medicine
hospice and palliative

Verbatim Response
Oncology Pharmacy
RADIATION ONCOLOGY
gyn oncology

Listing 3 VERBATIM RESPONSES TO REPORTED ADVERSE EVENTS, PRODUCT COMPLAINTS OR REQUESTS FOR MEDICAL INFORMATION

Verbatim Response
Answered incorrectly -- meant to select 'no questions'
dose titration, any specific guiediliness
How can I get a copy of the medication guide so I can better educate my patients?
HOW TO CONVERSION.
How to dose these medications when converting from other opiate short acting rx?
I asked the pharmacist at the time of prescribing.
I had questions regarding dosing, but they were answered by another physician in the office.
I have received guides in the past and have access at my office where I am not at this time. I have asked the representatives questions in the past that I do not presently remember. I do not have any questions at this moment but answered in that I have had questions in the past.
I have used these products for years, I DID have questions when I began initially using these products. I cannot recall particular questions right now.
It has been a long time since I prescribed the TIRF (Lazanda), so I would need to review both guides prior to prescribing it again. Once I have done so, I would not have any other questions.
More safety issues, and conversion issue questions
na
none
none sorry
none
NOT ENOUGH INFO RE TITRATION OF DOSING
opiods in conjunction with subsys safe and effective doses without causing respiratory depression, side effects that can occur other than respiratory depression
Please send me all the information and monthly update about these meds
Questions were answered by drug rep from Fentora. Question was regarding 3rd dose after taking 2nd dose 30 mins after 1st dose was ineffective.
Side effects on nteeth caries
specifics of opioid interaction
Subsys titration kit instructions and what is in the titration kit
the definition of opioid tolerant patient is confusing.

Verbatim Response
the source or data behind the information related to whether the different brand are equianalgesic or not
they were answered by the rep.
What are the available studies to demonstrate equitable dosing between the many TIRF medications?
what are the interactions with other meds in the cyp450 system?
What are the percentages of Cyp3A4 polymorphisms or any other polymorphism which are currently being investigated involving TIRF?
what dose of morphine is required to be considered opioid tolerant? Have questions about the conversion ratio among the medications
what is the optimal way to use Fentora
where do I accesss this info
Will there be indictations for other diagnoses?
would like conversion chart
none
none
none
none

TABLE 1.1 SURVEY ADMINISTRATION STATISTICS

Question	N	%
The number of invitations issued to prescribers	5108	
The number of reminder letters mailed to prescribers	11,986	
The number of respondents screened for participation	425 [1]	
The number of respondents eligible for participation	302	
The number of respondents eligible for participation who completed the survey	302	71.1
By Telephone	13	3.1
By Internet	289	68.0

[1] This is the denominator for the percentages in this table (N=425).

TABLE 1.2 TIME TO COMPLETE SURVEY (COMPLETERS ONLY)

Time to Complete Survey			
Summary Statistic	**Telephone**	**Internet**	**Total**
N	13	289	302
Mean (SD)	27.0 (3.16)	17.0 (9.75)	17.5 (9.77)
Minimum	21	5	5
Median	26.3	15.0	15.2
Maximum	34	109	109
Category	**Telephone**	**Internet**	**Total**
5 to <10 Minutes	0	47	47
10 to <15 Minutes	0	97	97
15 to <20 Minutes	0	70	70
20 to <25 Minutes	3	36	39
25 to <30 Minutes	9	22	31
30 Minutes or More	1	17	18

TABLE 1.3 SURVEY PARTICIPANT SCREENING RESULTS

Question	All Respondents N=425		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 1: Do you agree to participate in this survey?				
Yes	423	99.5	302	100.0
No [1]	2	0.5		
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.				
Yes [1]	17	4.0		
No	357	84.0	302	100.0
I don't know [1]	49	11.5		
Question not asked [2]	2	0.5		
Question 3: Are you enrolled in the TIRF REMS Access program?				
Yes [1]	308	72.5	302	100.0
No	24	5.6		
I don't know[1]	25	5.9		
Question not asked [3]	68	16.0		

Question	All Respondents N=425		Eligible and Complete Respondents N=302	
	N	%	N	%
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply. [3]				
Anesta LLC [1]	0	0.0		
Archimedes Pharma US Inc.[1]	0	0.0		
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	1	0.2		
Endo Pharmaceuticals Inc. [1]	0	0.0		
Galena Biopharma [1]	0	0.0		
Insys Therapeutics [1]	0	0.0		
Mallinckrodt[1]	0	0.0		
McKesson Specialty Care Solutions [1]	0	0.0		
Meda Pharmaceuticals [1]	0	0.0		
Mylan, Inc.[1]	1	0.2		
Par Pharmaceutical, Inc.[1]	0	0.0		
ProStrakan, Inc.[1]	0	0.0		
RelayHealth [1]	0	0.0		
Teva Pharmaceuticals, Ltd.[1]	2	0.5		
United BioSource Corporation [1]	0	0.0		
FDA [1]	0	0.0		
None of these apply [4]	302	71.1	302	100.0
I don't know [1]	1	0.2		
Prefer not to answer [1]	1	0.2		
Question not asked [2]	117	27.5		

[1] Ineligible to participate in the survey.

[2] Question not asked due to a previous question elimination.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Ineligible if selected in addition to another response.

TABLE 2 DESCRIPTION OF ELIGIBLE AND COMPLETE RESPONDENTS

Question	Eligible and Complete Respondents N=302	
	N	%
Question 29: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?		
None	54	17.9
1 – 2 times per month	173	57.3
3 – 5 times per month	44	14.6
More than 5 times per month	18	6.0
I don't remember	13	4.3
Question 30: Please select the TIRF medicines that you have prescribed within the last 6 months: (select all that apply)		
Abstral®	10	4.0
Actiq® or generic Actiq®	184	74.2
Fentora®	145	58.5
Lazanda®	16	6.5
Onsolis®	4	1.6
Subsys®	56	22.6
N/A (answered ***None*** to Question 29)	54	
Question 31: What is your gender?		
Male	197	65.2
Female	103	34.1
Prefer not to answer	2	0.7
Question 32: What is your medical degree?		
MD	182	60.3
DO	22	7.3
Nurse Practitioner	66	21.9
Physician Assistant	30	9.9
Prefer not to answer	2	0.7

Question	Eligible and Complete Respondents N=302	
	N	%
Question 33: In total, how many years have you been practicing medicine, since completing your education? (MDs and DOs, only) [1]		
Less than 3 years	28	9.3
3 - 5 years	49	16.2
6 - 10 years	55	18.2
11 - 15 years	51	16.9
More than 15 years	117	38.7
Prefer not to answer	2	0.7
Question 35: What is your medical specialty?		
Oncology	69	22.8
Primary care	30	9.9
Pain management	148	49.0
Other (please specify) [2]	53	17.5

[1] This question is presented only to the sub-group of prescribers who answered "MD", "DO", or "Prefer not to answer" in Question 32. Percentages are based on the number of prescribers to whom this question was presented.

[2] Other medical specialties are presented in Listing 3.

TABLE 2.1 GEOGRAPHIC DISTRIBUTION (BASED ON QUESTION 31 – IN WHICH STATE OR US TERRITORY DO YOU PRACTICE)

Geographic Region [1]	Eligible and Complete Respondents N=302		Enrolled in TIRF REMS Access Program on 19Oct2013 N=9042	
	N	%	N	%
Northeast	83	27.5	2063	22.8
Midwest	46	15.2	1534	17.0
South	100	33.1	3010	33.3
West	71	23.5	2432	26.9
Other	0	0.0	3	0.0
Prefer not to answer	2	0.7	0	0.0

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

TABLE 3 RESPONSES TO THE QUESTIONS ABOUT THE SAFE USE OF TIRF MEDICINES

Question	Eligible and Complete Respondents N=302	
	N	%
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer		
True [1]	273	90.4
False	24	7.9
I don't know	5	1.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
False [1]	266	88.1
True	28	9.3
I don't know	8	2.6
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
False [1]	248	82.1
True	39	12.9
I don't know	15	5.0
Question 6: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
6a: A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.		
False [1]	183	60.6
True	105	34.8
I don't know	14	4.6

Question	Eligible and Complete Respondents N=302	
	N	%
6b: A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
False [1]	196	64.9
True	86	28.5
I don't know	20	6.6
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [1]	265	87.7
False	32	10.6
I don't know	5	1.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [1]	283	93.7
False	3	1.0
I don't know	16	5.3
7c: TIRF medicines may be used in treat opioid non-tolerant patients.		
False [1]	242	80.1
True	43	14.2
I don't know	17	5.6
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True [1]	244	80.8
False	52	17.2
I don't know	6	2.0

Question	Eligible and Complete Respondents N=302	
	N	%
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [1]	299	99.0
False	2	0.7
I don't know	1	0.3
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
8a: A personal history of psychiatric illness		
Yes [1]	250	82.8
No	31	10.3
I don't know	21	7.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [1]	299	99.0
No	2	0.7
I don't know	1	0.3
8c: A family history of asthma		
No [1]	271	89.7
Yes	12	4.0
I don't know	19	6.3
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.		
9a: Acute or postoperative pain		
No [1]	281	93.0
Yes	17	5.6
I don't know	4	1.3

Question	Eligible and Complete Respondents N=302	
	N	%
9b: Headache or migraine pain		
No [1]	279	92.4
Yes	20	6.6
I don't know	3	1.0
9c: Dental pain		
No [1]	292	96.7
Yes	5	1.7
I don't know	5	1.7
9d: Breakthrough pain from cancer		
Yes [1]	279	92.4
No	22	7.3
I don't know	1	0.3
9e: Chronic non-cancer pain		
No [1]	178	58.9
Yes	119	39.4
I don't know	5	1.7
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True [1]	291	96.4
False	9	3.0
I don't know	2	0.7
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
False [1]	279	92.4
True	16	5.3
I don't know	7	2.3

Question	Eligible and Complete Respondents N=302	
	N	%
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True [1]	286	94.7
False	7	2.3
I don't know	9	3.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True [1]	274	90.7
False	16	5.3
I don't know	12	4.0
Quesiton 11: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True [1]	207	68.5
False	64	21.2
I don't know	31	10.3
11b: 60 mg oral morphine/day		
True [1]	269	89.1
False	16	5.3
I don't know	17	5.6
11c: 30 mg oral oxycodone/day		
True [1]	230	76.2
False	47	15.6
I don't know	25	8.3
11d: 25 mcg transdermal fentanyl/hour		
True [1]	244	80.8
False	34	11.3
I don't know	24	7.9

Question	Eligible and Complete Respondents N=302	
	N	%
11e: 25 mg oral oxymorphone/day		
True [1]	211	69.9
False	39	12.9
I don't know	52	17.2
11f: An equianalgesic dose of another oral opioid		
True [1]	199	65.9
False	68	22.5
I don't know	35	11.6
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	199	65.9
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	36	11.9
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	12	4.0
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	28	9.3
I don’t know	27	8.9

Question	Eligible and Complete Respondents N=302	
	N	%
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	225	74.5
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	6	2.0
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25	8.3
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	34	11.3
I don't know	12	4.0
Question 15: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.		
The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance. [1]	254	84.1
An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	37	12.3
The dose that the prescriber believes is appropriate based on their clinical experience.	8	2.6
The median available dose.	1	0.3
I don't know	2	0.7

Question	Eligible and Complete Respondents N=302	
	N	%
Question 16: A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.		
Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines. [1]	205	67.9
Take another (identical) dose of the TIRF medicine immediately.	73	24.2
Take a dose of an alternative rescue medicine.	16	5.3
Double the dose and take immediately.	3	1.0
I don't know	5	1.7
Question 17: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.		
Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression. [1]	225	74.5
The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	11	3.6
There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	3	1.0
The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.	13	4.3
I don't know	50	16.6
Question 18: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select "True," "False," or "I don't know" for each of the following counseling statements.		
18a: TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.		
True [1]	298	98.7
False	1	0.3
I don't know	3	1.0

Question	Eligible and Complete Respondents N=302	
	N	%
18b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.		
True [1]	278	92.1
False	16	5.3
I don't know	8	2.6
18c: Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine.		
False [1]	175	57.9
True	95	31.5
I don't know	32	10.6
18d: Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.		
True [1]	299	99.0
False	3	1.0
I don't know	0	0.0
Question 19: Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?		
Yes [1]	105	34.8
No	160	53.0
I don't know	37	12.3

[1] Correct response

TABLE 4 RESPONSES TO QUESTIONS ABOUT THE TIRF EDUCATIONAL MATERIALS AND THE TIRF PATIENT-PRESCRIBER AGREEMENT FORM

Question	Eligible and Complete Respondents N=302	
	N	%
Question 20: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?		
Yes	282	93.4
No	6	2.0
I don't know	14	4.6
Question 21: Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?[2]		
Yes	243	86.2
No	33	11.7
I don't know	6	2.1
N/A (answered ***No*** or ***I don't know*** to Question 20)	20	
Question 22: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?		
Yes	273	90.4
No	8	2.6
I don't know	21	7.0
Question 23: Did you read the Medication Guide for the TIRF medicine(s) that you prescribe? [2]		
Yes	246	90.1
No	24	8.8
I don't know	3	1.1
N/A (answered ***No*** or ***I don't know*** to Question 22)	29	
Question 24: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes[1]	37	12.3
No	243	80.5
I don't know	22	7.3

Question	Eligible and Complete Respondents N=302	
	N	%
Question 26: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?		
Yes	262	86.8
No	25	8.3
I don't know	15	5.0
Question 27: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her? [2]		
Yes	242	92.4
No	12	4.6
I don't know	8	3.1
N/A (answered ***No*** or ***I don't know*** to Question 26)	40	
Question 28: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?		
Yes	243	80.5
No	34	11.3
I don't know	25	8.3

[1] Verbatim texts for questions about the information in the Full Prescribing Information are presented in Listing 1.

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

TABLE 5 RESPONSES TO QUESTIONS ABOUT ACTIVITIES WHEN PRESCRIBING TIRF MEDICINES

Question	Prescribers N=302	
	N	%
Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."		
12a: Ask patients (or their caregivers) about the presence of children in the home		
Always	170	56.3
Only with the first prescription	70	23.2
Sometimes	48	15.9
Never	11	3.6
I don't know	3	1.0
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else		
Always	239	79.1
Only with the first prescription	37	12.3
Sometimes	19	6.3
Never	5	1.7
I don't know	2	0.7
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal		
Always	197	65.2
Only with the first prescription	63	20.9
Sometimes	31	10.3
Never	8	2.6
I don't know	3	1.0

Question	Prescribers N=302	
	N	%
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure		
Always	220	72.8
Only with the first prescription	46	15.2
Sometimes	28	9.3
Never	5	1.7
I don't know	3	1.0
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines		
Always	187	61.9
Only with the first prescription	62	20.5
Sometimes	37	12.3
Never	12	4.0
I don't know	4	1.3
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine		
Always	142	47.0
Only with the first prescription	108	35.8
Sometimes	26	8.6
Never	20	6.6
I don't know	6	2.0

TABLE 6.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer		
True [1]	273	90.4 (86.5, 93.5)
False	24	7.9
I don't know	5	1.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
False [1]	266	88.1 (83.9, 91.5)
True	28	9.3
I don't know	8	2.6
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
False [1]	248	82.1 (77.3, 86.3)
True	39	12.9
I don't know	15	5.0

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [1]	265	87.7 (83.5, 91.2)
False	32	10.6
I don't know	5	1.7
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [1]	283	93.7 (90.3, 96.2)
False	3	1.0
I don't know	16	5.3
7c: TIRF medicines may be used in opioid non-tolerant patients.		
False [1]	242	80.1 (75.2, 84.5)
True	43	14.2
I don't know	17	5.6
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True [1]	244	80.8 (75.9, 85.1)
False	52	17.2
I don't know	6	2.0

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 6.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer				
True [1]	243	91.0 (86.9, 94.2)	30	85.7 (69.7, 95.2)
False	22	8.2	2	5.7
I don't know	2	0.7	3	8.6
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	238	89.1 (84.8, 92.6)	28	80.0 (63.1, 91.6)
True	25	9.4	3	8.6
I don't know	4	1.5	4	11.4

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	223	83.5 (78.5, 87.8)	25	71.4 (53.7, 85.4)
True	35	13.1	4	11.4
I don't know	9	3.4	6	17.1
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	237	88.8 (84.3, 92.3)	28	80.0 (63.1, 91.6)
False	26	9.7	6	17.1
I don't know	4	1.5	1	2.9
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	252	94.4 (90.9, 96.8)	31	88.6 (73.3, 96.8)
False	3	1.1	0	0.0
I don't know	12	4.5	4	11.4
7c: TIRF medicines may be used in opioid non-tolerant patients.				
False [1]	218	81.6 (76.5, 86.1)	24	68.6 (50.7, 83.1)
True	38	14.2	5	14.3
I don't know	11	4.1	6	17.1

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	218	81.6 (76.5, 86.1)	26	74.3 (56.7, 87.5)
False	45	16.9	7	20.0
I don't know	4	1.5	2	5.7

[1] Correct response

TABLE 6.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer								
True [1]	160	87.9 (82.3, 92.3)	21	95.5 (77.2, 99.9)	63	95.5 (87.3, 99.1)	27	90.0 (73.5, 97.9)
False	19	10.4	1	4.5	3	4.5	1	3.3
I don't know	3	1.6	0	0.0	0	0.0	2	6.7

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	158	86.8 (81.0, 91.4)	19	86.4 (65.1, 97.1)	60	90.9 (81.3, 96.6)	27	90.0 (73.5, 97.9)
True	17	9.3	3	13.6	6	9.1	2	6.7
I don't know	7	3.8	0	0.0	0	0.0	1	3.3
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	146	80.2 (73.7, 85.7)	18	81.8 (59.7, 94.8)	58	87.9 (77.5, 94.6)	24	80.0 (61.4, 92.3)
True	28	15.4	3	13.6	4	6.1	4	13.3
I don't know	8	4.4	1	4.5	4	6.1	2	6.7

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	160	87.9 (82.3, 92.3)	20	90.9 (70.8, 98.9)	53	80.3 (68.7, 89.1)	30	100.0 (88.4, 100.0)
False	19	10.4	2	9.1	11	16.7	0	0.0
I don't know	3	1.6	0	0.0	2	3.0	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	173	95.1 (90.8, 97.7)	21	95.5 (77.2, 99.9)	59	89.4 (79.4, 95.6)	28	93.3 (77.9, 99.2)
False	2	1.1	1	4.5	0	0.0	0	0.0
I don't know	7	3.8	0	0.0	7	10.6	2	6.7

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	146	80.2 (73.7, 85.7)	20	90.9 (70.8, 98.9)	49	74.2 (62.0, 84.2)	25	83.3 (65.3, 94.4)
True	27	14.8	2	9.1	11	16.7	3	10.0
I don't know	9	4.9	0	0.0	6	9.1	2	6.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	149	81.9 (75.5, 87.2)	14	63.6 (40.7, 82.8)	54	81.8 (70.4, 90.2)	25	83.3 (65.3, 94.4)
False	28	15.4	8	36.4	11	16.7	5	16.7
I don't know	5	2.7	0	0.0	1	1.5	0	0.0

[1] Correct response

TABLE 6.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:						
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer						
True [1]	38	80.9 (66.7, 90.9)	155	92.8 (87.8, 96.2)	68	90.7 (81.7, 96.2)
False	7	14.9	11	6.6	6	8.0
I don't know	2	4.3	1	0.6	1	1.3
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before						
False [1]	40	85.1 (71.7, 93.8)	149	89.2 (83.5, 93.5)	70	93.3 (85.1, 97.8)
True	2	4.3	15	9.0	5	6.7
I don't know	5	10.6	3	1.8	0	0.0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy						
False [1]	38	80.9 (66.7, 90.9)	139	83.2 (76.7, 88.6)	64	85.3 (75.3, 92.4)
True	5	10.6	20	12.0	9	12.0
I don't know	4	8.5	8	4.8	2	2.7

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.						
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.						
True [1]	39	83.0 (69.2, 92.4)	145	86.8 (80.7, 91.6)	70	93.3 (85.1, 97.8)
False	7	14.9	18	10.8	5	6.7
I don't know	1	2.1	4	2.4	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.						
True [1]	44	93.6 (82.5, 98.7)	157	94.0 (89.3, 97.1)	69	92.0 (83.4, 97.0)
False	1	2.1	1	0.6	1	1.3
I don't know	2	4.3	9	5.4	5	6.7
7c: TIRF medicines may be used in opioid non-tolerant patients.						
False [1]	36	76.6 (62.0, 87.7)	134	80.2 (73.4, 86.0)	63	84.0 (73.7, 91.4)
True	9	19.1	22	13.2	10	13.3
I don't know	2	4.3	11	6.6	2	2.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.						
True [1]	40	85.1 (71.7, 93.8)	130	77.8 (70.8, 83.9)	62	82.7 (72.2, 90.4)
False	7	14.9	31	18.6	13	17.3
I don't know	0	0.0	6	3.6	0	0.0

[1] Correct response

TABLE 6.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer				
True [1]	261	90.3 (86.3, 93.5)	12	92.3 (64.0, 99.8)
False	24	8.3	0	0.0
I don't know	4	1.4	1	7.7
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
False [1]	259	89.6 (85.5, 92.9)	7	53.8 (25.1, 80.8)
True	22	7.6	6	46.2
I don't know	8	2.8	0	0.0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
False [1]	241	83.4 (78.6, 87.5)	7	53.8 (25.1, 80.8)
True	34	11.8	5	38.5
I don't know	14	4.8	1	7.7

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True [1]	254	87.9 (83.6, 91.4)	11	84.6 (54.6, 98.1)
False	30	10.4	2	15.4
I don't know	5	1.7	0	0.0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True [1]	270	93.4 (89.9, 96.0)	13	100.0 (75.3, 100.0)
False	3	1.0	0	0.0
I don't know	16	5.5	0	0.0
7c: TIRF medicines may be used in opioid non-tolerant patients.				
False [1]	233	80.6 (75.6, 85.0)	9	69.2 (38.6, 90.9)
True	41	14.2	2	15.4
I don't know	15	5.2	2	15.4
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True [1]	232	80.3 (75.2, 84.7)	12	92.3 (64.0, 99.8)
False	51	17.6	1	7.7
I don't know	6	2.1	0	0.0

[1] Correct response

TABLE 6.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer								
True [1]	26	92.9 (76.5, 99.1)	40	81.6 (68.0, 91.2)	97	91.5 (84.5, 96.0)	108	92.3 (85.9, 96.4)
False	1	3.6	7	14.3	8	7.5	8	6.8
I don't know	1	3.6	2	4.1	1	0.9	1	0.9

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	25	89.3 (71.8, 97.7)	43	87.8 (75.2, 95.4)	90	84.9 (76.6, 91.1)	106	90.6 (83.8, 95.2)
True	2	7.1	5	10.2	11	10.4	10	8.5
I don't know	1	3.6	1	2.0	5	4.7	1	0.9
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	24	85.7 (67.3, 96.0)	43	87.8 (75.2, 95.4)	83	78.3 (69.2, 85.7)	96	82.1 (73.9, 88.5)
True	2	7.1	3	6.1	15	14.2	19	16.2
I don't know	2	7.1	3	6.1	8	7.5	2	1.7
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	24	85.7 (67.3, 96.0)	41	83.7 (70.3, 92.7)	91	85.8 (77.7, 91.9)	107	91.5 (84.8, 95.8)
False	4	14.3	8	16.3	12	11.3	8	6.8
I don't know	0	0.0	0	0.0	3	2.8	2	1.7

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	25	89.3 (71.8, 97.7)	45	91.8 (80.4, 97.7)	99	93.4 (86.9, 97.3)	112	95.7 (90.3, 98.6)
False	0	0.0	1	2.0	2	1.9	0	0.0
I don't know	3	10.7	3	6.1	5	4.7	5	4.3
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	21	75.0 (55.1, 89.3)	37	75.5 (61.1, 86.7)	81	76.4 (67.2, 84.1)	101	86.3 (78.7, 92.0)
True	5	17.9	9	18.4	16	15.1	13	11.1
I don't know	2	7.1	3	6.1	9	8.5	3	2.6
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	21	75.0 (55.1, 89.3)	38	77.6 (63.4, 88.2)	92	86.8 (78.8, 92.6)	91	77.8 (69.2, 84.9)
False	7	25.0	11	22.4	11	10.4	23	19.7
I don't know	0	0.0	0	0.0	3	2.8	3	2.6

[1] Correct response

TABLE 6.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS. SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 5: Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:								
5a: Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer								
True [1]	52	96.3 (87.3, 99.5)	161	93.1 (88.2, 96.4)	36	81.8 (67.3, 91.8)	14	77.8 (52.4, 93.6)
False	1	1.9	11	6.4	7	15.9	3	16.7
I don't know	1	1.9	1	0.6	1	2.3	1	5.6

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before								
False [1]	44	81.5 (68.6, 90.7)	159	91.9 (86.8, 95.5)	37	84.1 (69.9, 93.4)	16	88.9 (65.3, 98.6)
True	7	13.0	11	6.4	6	13.6	2	11.1
I don't know	3	5.6	3	1.7	1	2.3	0	0.0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy								
False [1]	44	81.5 (68.6, 90.7)	147	85.0 (78.8, 89.9)	32	72.7 (57.2, 85.0)	16	88.9 (65.3, 98.6)
True	6	11.1	18	10.4	9	20.5	2	11.1
I don't know	4	7.4	8	4.6	3	6.8	0	0.0
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.								
True [1]	47	87.0 (75.1, 94.6)	152	87.9 (82.0, 92.3)	41	93.2 (81.3, 98.6)	15	83.3 (58.6, 96.4)
False	6	11.1	17	9.8	3	6.8	3	16.7
I don't know	1	1.9	4	2.3	0	0.0	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.								
True [1]	52	96.3 (87.3, 99.5)	163	94.2 (89.6, 97.2)	40	90.9 (78.3, 97.5)	17	94.4 (72.7, 99.9)
False	1	1.9	0	0.0	1	2.3	1	5.6
I don't know	1	1.9	10	5.8	3	6.8	0	0.0
7c: TIRF medicines may be used in opioid non-tolerant patients.								
False [1]	42	77.8 (64.4, 88.0)	144	83.2 (76.8, 88.5)	37	84.1 (69.9, 93.4)	13	72.2 (46.5, 90.3)
True	7	13.0	20	11.6	7	15.9	2	11.1
I don't know	5	9.3	9	5.2	0	0.0	3	16.7
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.								
True [1]	42	77.8 (64.4, 88.0)	143	82.7 (76.2, 88.0)	38	86.4 (72.6, 94.8)	11	61.1 (35.7, 82.7)
False	10	18.5	26	15.0	6	13.6	7	38.9
I don't know	2	3.7	4	2.3	0	0.0	0	0.0

[1] Correct response

TABLE 6.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

Demonstrated Understanding	Eligible and Complete Respondents N=302	
	N	%
0 correct responses	1	0.3
1 correct response	2	0.7
2 correct responses	1	0.3
3 correct responses	7	2.3
4 correct responses	23	7.6
5 correct responses	41	13.6
6 correct responses	90	29.8
7 correct responses	137	45.4
Average number of correct responses	6.0	(5.8, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	%	N	%
0 correct responses	0	0.0	1	2.9
1 correct response	1	0.4	1	2.9
2 correct responses	1	0.4	0	0.0
3 correct responses	4	1.5	3	8.6
4 correct responses	20	7.5	3	8.6
5 correct responses	36	13.5	5	14.3
6 correct responses	81	30.3	9	25.7
7 correct responses	124	46.4	13	37.1
Average number of correct responses	6.1	(5.9, 7.0) [1]	5.5	(4.8, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	%	N	%	N	%	N	%
0 correct responses	1	0.5	0	0.0	0	0.0	0	0.0
1 correct response	1	0.5	0	0.0	1	1.5	0	0.0
2 correct responses	1	0.5	0	0.0	0	0.0	0	0.0
3 correct responses	6	3.3	0	0.0	1	1.5	0	0.0
4 correct responses	12	6.6	2	9.1	7	10.6	2	6.7
5 correct responses	26	14.3	3	13.6	8	12.1	4	13.3
6 correct responses	52	28.6	9	40.9	19	28.8	10	33.3
7 correct responses	83	45.6	8	36.4	30	45.5	14	46.7
Average number of correct responses	6.0	(5.7, 7.0) [1]	6.0	(5.2, 7.0) [1]	6.0	(5.5, 7.0) [1]	6.2	(5.5, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	%	N	%	N	%
0 correct responses	0	0.0	1	0.6	0	0.0
1 correct response	1	2.1	0	0.0	0	0.0
2 correct responses	1	2.1	0	0.0	0	0.0
3 correct responses	2	4.3	3	1.8	2	2.7
4 correct responses	1	2.1	19	11.4	3	4.0
5 correct responses	8	17.0	20	12.0	8	10.7
6 correct responses	16	34.0	44	26.3	26	34.7
7 correct responses	18	38.3	80	47.9	36	48.0
Average number of correct responses	5.9	(5.3, 7.0) [1]	6.0	(5.7, 7.0) [1]	6.2	(5.7, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=289		S-5b Telephone N=13	
	N	%	N	%
0 correct responses	1	0.3	0	0.0
1 correct response	1	0.3	1	7.7
2 correct responses	1	0.3	0	0.0
3 correct responses	7	2.4	0	0.0
4 correct responses	23	8.0	0	0.0
5 correct responses	36	12.5	5	38.5
6 correct responses	86	29.8	4	30.8
7 correct responses	134	46.4	3	23.1
Average number of correct responses	6.1	(5.8, 7.0) [1]	5.5	(4.4, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	0.9	0	0.0
1 correct response	0	0.0	1	2.0	1	0.9	0	0.0
2 correct responses	0	0.0	0	0.0	1	0.9	0	0.0
3 correct responses	1	3.6	1	2.0	2	1.9	3	2.6
4 correct responses	5	17.9	3	6.1	7	6.6	8	6.8
5 correct responses	1	3.6	10	20.4	18	17.0	12	10.3
6 correct responses	9	32.1	17	34.7	26	24.5	38	32.5
7 correct responses	12	42.9	17	34.7	50	47.2	56	47.9
Average number of correct responses	5.9	(5.2, 7.0)[1]	5.9	(5.3, 7.0)[1]	6.0	(5.6, 7.0)[1]	6.2	(5.8, 7.0)[1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 6.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #1

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	1	0.6	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	2	11.1
2 correct responses	0	0.0	0	0.0	1	2.3	0	0.0
3 correct responses	2	3.7	2	1.2	1	2.3	0	0.0
4 correct responses	6	11.1	10	5.8	5	11.4	0	0.0
5 correct responses	8	14.8	21	12.1	4	9.1	3	16.7
6 correct responses	13	24.1	55	31.8	15	34.1	6	33.3
7 correct responses	25	46.3	84	48.6	18	40.9	7	38.9
Average number of correct responses	6.0	(5.4, 7.0) [1]	6.2	(5.9, 7.0) [1]	5.9	(5.3, 7.0) [1]	5.7	(4.7, 7.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

Client: TRIG Project: TIRF Wave 2

Report Run Date and Time: 11/13/2013 1:28:00 PM

TABLE 7.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.		
9a: Acute or postoperative pain		
No [1]	281	93.0 (89.6, 95.6)
Yes	17	5.6
I don't know	4	1.3
9b: Headache or migraine pain		
No [1]	279	92.4 (88.8, 95.1)
Yes	20	6.6
I don't know	3	1.0
9c: Dental pain		
No [1]	292	96.7 (94.0, 98.4)
Yes	5	1.7
I don't know	5	1.7

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
9d: Breakthrough pain from cancer		
Yes [1]	279	92.4 (88.8, 95.1)
No	22	7.3
I don't know	1	0.3
9e: Chronic non-cancer pain		
No [1]	178	58.9 (53.2, 64.5)
Yes	119	39.4
I don't know	5	1.7
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	199	65.9 (60.2, 71.2)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	36	11.9
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	12	4.0
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	28	9.3
I don't know	27	8.9

[1] Correct response

[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 7.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.				
9a: Acute or postoperative pain				
No [1]	248	92.9 (89.1, 95.7)	33	94.3 (80.8, 99.3)
Yes	15	5.6	2	5.7
I don't know	4	1.5	0	0.0
9b: Headache or migraine pain				
No [1]	246	92.1 (88.2, 95.1)	33	94.3 (80.8, 99.3)
Yes	18	6.7	2	5.7
I don't know	3	1.1	0	0.0

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
9c: Dental pain				
No [1]	258	96.6 (93.7, 98.4)	34	97.1 (85.1, 99.9)
Yes	5	1.9	0	0.0
I don't know	4	1.5	1	2.9
9d: Breakthrough pain from cancer				
Yes [1]	248	92.9 (89.1, 95.7)	31	88.6 (73.3, 96.8)
No	18	6.7	4	11.4
I don't know	1	0.4	0	0.0
9e: Chronic non-cancer pain				
No [1]	158	59.2 (53.0, 65.1)	20	57.1 (39.4, 73.7)
Yes	105	39.3	14	40.0
I don't know	4	1.5	1	2.9

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	178	66.7 (60.7, 72.3)	21	60.0 (42.1, 76.1)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	31	11.6	5	14.3
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	12	4.5	0	0.0
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	25	9.4	3	8.6
I don't know	21	7.9	6	17.1

[1] Correct response

TABLE 7.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.								
9a: Acute or postoperative pain								
No [1]	169	92.9 (88.1, 96.1)	21	95.5 (77.2, 99.9)	59	89.4 (79.4, 95.6)	30	100.0 (88.4, 100.0)
Yes	11	6.0	0	0.0	6	9.1	0	0.0
I don't know	2	1.1	1	4.5	1	1.5	0	0.0

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	164	90.1 (84.8, 94.0)	21	95.5 (77.2, 99.9)	64	97.0 (89.5, 99.6)	28	93.3 (77.9, 99.2)
Yes	17	9.3	0	0.0	1	1.5	2	6.7
I don't know	1	0.5	1	4.5	1	1.5	0	0.0
9c: Dental pain								
No [1]	175	96.2 (92.2, 98.4)	21	95.5 (77.2, 99.9)	64	97.0 (89.5, 99.6)	30	100.0 (88.4, 100.0)
Yes	4	2.2	1	4.5	0	0.0	0	0.0
I don't know	3	1.6	0	0.0	2	3.0	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	168	92.3 (87.4, 95.7)	21	95.5 (77.2, 99.9)	60	90.9 (81.3, 96.6)	28	93.3 (77.9, 99.2)
No	13	7.1	1	4.5	6	9.1	2	6.7
I don't know	1	0.5	0	0.0	0	0.0	0	0.0

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	109	59.9 (52.4, 67.1)	13	59.1 (36.4, 79.3)	35	53.0 (40.3, 65.4)	20	66.7 (47.2, 82.7)
Yes	70	38.5	9	40.9	30	45.5	9	30.0
I don't know	3	1.6	0	0.0	1	1.5	1	3.3
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.								
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	123	67.6 (60.3, 74.3)	12	54.5 (32.2, 75.6)	43	65.2 (52.4, 76.5)	21	70.0 (50.6, 85.3)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	19	10.4	4	18.2	7	10.6	5	16.7

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	10	5.5	0	0.0	1	1.5	1	3.3
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	16	8.8	2	9.1	6	9.1	3	10.0
I don't know	14	7.7	4	18.2	9	13.6	0	0.0

[1] Correct response

TABLE 7.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.						
9a: Acute or postoperative pain						
No [1]	45	95.7 (85.5, 99.5)	154	92.2 (87.1, 95.8)	70	93.3 (85.1, 97.8)
Yes	1	2.1	11	6.6	4	5.3
I don't know	1	2.1	2	1.2	1	1.3
9b: Headache or migraine pain						
No [1]	44	93.6 (82.5, 98.7)	155	92.8 (87.8, 96.2)	67	89.3 (80.1, 95.3)
Yes	3	6.4	10	6.0	7	9.3
I don't know	0	0.0	2	1.2	1	1.3
9c: Dental pain						
No [1]	44	93.6 (82.5, 98.7)	162	97.0 (93.2, 99.0)	73	97.3 (90.7, 99.7)
Yes	1	2.1	2	1.2	2	2.7
I don't know	2	4.3	3	1.8	0	0.0

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9d: Breakthrough pain from cancer						
Yes [1]	45	95.7 (85.5, 99.5)	160	95.8 (91.6, 98.3)	61	81.3 (70.7, 89.4)
No	2	4.3	6	3.6	14	18.7
I don't know	0	0.0	1	0.6	0	0.0
9e: Chronic non-cancer pain						
No [1]	31	66.0 (50.7, 79.1)	92	55.1 (47.2, 62.8)	45	60.0 (48.0, 71.1)
Yes	15	31.9	72	43.1	29	38.7
I don't know	1	2.1	3	1.8	1	1.3

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.						
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	22	46.8 (32.1, 61.9)	120	71.9 (64.4, 78.5)	51	68.0 (56.2, 78.3)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	8	17.0	15	9.0	11	14.7
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	3	6.4	7	4.2	0	0.0
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	6	12.8	13	7.8	7	9.3
I don't know	8	17.0	12	7.2	6	8.0

[1] Correct response

TABLE 7.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.				
9a: Acute or postoperative pain				
No [1]	269	93.1 (89.5, 95.7)	12	92.3 (64.0, 99.8)
Yes	16	5.5	1	7.7
I don't know	4	1.4	0	0.0
9b: Headache or migraine pain				
No [1]	266	92.0 (88.3, 94.9)	13	100.0 (75.3, 100.0)
Yes	20	6.9	0	0.0
I don't know	3	1.0	0	0.0
9c: Dental pain				
No [1]	279	96.5 (93.7, 98.3)	13	100.0 (75.3, 100.0)
Yes	5	1.7	0	0.0
I don't know	5	1.7	0	0.0

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
9d: Breakthrough pain from cancer				
Yes [1]	266	92.0 (88.3, 94.9)	13	100.0 (75.3, 100.0)
No	22	7.6	0	0.0
I don't know	1	0.3	0	0.0
9e: Chronic non-cancer pain				
No [1]	168	58.1 (52.2, 63.9)	10	76.9 (46.2, 95.0)
Yes	116	40.1	3	23.1
I don't know	5	1.7	0	0.0

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	193	66.8 (61.0, 72.2)	6	46.2 (19.2, 74.9)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	34	11.8	2	15.4
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	10	3.5	2	15.4
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	26	9.0	2	15.4
I don't know	26	9.0	1	7.7

[1] Correct response

TABLE 7.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.								
9a: Acute or postoperative pain								
No [1]	27	96.4 (81.7, 99.9)	43	87.8 (75.2, 95.4)	99	93.4 (86.9, 97.3)	110	94.0 (88.1, 97.6)
Yes	0	0.0	5	10.2	5	4.7	7	6.0
I don't know	1	3.6	1	2.0	2	1.9	0	0.0

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	27	96.4 (81.7, 99.9)	46	93.9 (83.1, 98.7)	98	92.5 (85.7, 96.7)	106	90.6 (83.8, 95.2)
Yes	0	0.0	3	6.1	6	5.7	11	9.4
I don't know	1	3.6	0	0.0	2	1.9	0	0.0
9c: Dental pain								
No [1]	27	96.4 (81.7, 99.9)	48	98.0 (89.1, 99.9)	101	95.3 (89.3, 98.5)	114	97.4 (92.7, 99.5)
Yes	1	3.6	0	0.0	1	0.9	3	2.6
I don't know	0	0.0	1	2.0	4	3.8	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	27	96.4 (81.7, 99.9)	45	91.8 (80.4, 97.7)	97	91.5 (84.5, 96.0)	108	92.3 (85.9, 96.4)
No	1	3.6	4	8.2	8	7.5	9	7.7
I don't know	0	0.0	0	0.0	1	0.9	0	0.0

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	20	71.4 (51.3, 86.8)	31	63.3 (48.3, 76.6)	68	64.2 (54.3, 73.2)	57	48.7 (39.4, 58.1)
Yes	7	25.0	17	34.7	35	33.0	60	51.3
I don't know	1	3.6	1	2.0	3	2.8	0	0.0
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.								
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	21	75.0 (55.1, 89.3)	33	67.3 (52.5, 80.1)	63	59.4 (49.5, 68.9)	81	69.2 (60.0, 77.4)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	1	3.6	5	10.2	16	15.1	13	11.1

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	2	7.1	1	2.0	6	5.7	3	2.6
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	1	3.6	3	6.1	12	11.3	12	10.3
I don't know	3	10.7	7	14.3	9	8.5	8	6.8

[1] Correct response

TABLE 7.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS. SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.								
9a: Acute or postoperative pain								
No [1]	50	92.6 (82.1, 97.9)	164	94.8 (90.4, 97.6)	38	86.4 (72.6, 94.8)	17	94.4 (72.7, 99.9)
Yes	3	5.6	7	4.0	6	13.6	1	5.6
I don't know	1	1.9	2	1.2	0	0.0	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9b: Headache or migraine pain								
No [1]	51	94.4 (84.6, 98.8)	161	93.1 (88.2, 96.4)	38	86.4 (72.6, 94.8)	16	88.9 (65.3, 98.6)
Yes	2	3.7	10	5.8	6	13.6	2	11.1
I don't know	1	1.9	2	1.2	0	0.0	0	0.0
9c: Dental pain								
No [1]	52	96.3 (87.3, 99.5)	169	97.7 (94.2, 99.4)	42	95.5 (84.5, 99.4)	17	94.4 (72.7, 99.9)
Yes	0	0.0	2	1.2	2	4.5	1	5.6
I don't know	2	3.7	2	1.2	0	0.0	0	0.0
9d: Breakthrough pain from cancer								
Yes [1]	45	83.3 (70.7, 92.1)	161	93.1 (88.2, 96.4)	43	97.7 (88.0, 99.9)	17	94.4 (72.7, 99.9)
No	8	14.8	12	6.9	1	2.3	1	5.6
I don't know	1	1.9	0	0.0	0	0.0	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
9e: Chronic non-cancer pain								
No [1]	42	77.8 (64.4, 88.0)	102	59.0 (51.2, 66.4)	22	50.0 (34.6, 65.4)	7	38.9 (17.3, 64.3)
Yes	10	18.5	69	39.9	22	50.0	11	61.1
I don't know	2	3.7	2	1.2	0	0.0	0	0.0
Question 13: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.								
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks. [1]	39	72.2 (58.4, 83.5)	112	64.7 (57.1, 71.8)	26	59.1 (43.2, 73.7)	16	88.9 (65.3, 98.6)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	5	9.3	23	13.3	6	13.6	1	5.6

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	2	3.7	6	3.5	2	4.5	1	5.6
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	3	5.6	16	9.2	7	15.9	0	0.0
I don't know	5	9.3	16	9.2	3	6.8	0	0.0

[1] Correct response

TABLE 7.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 2: TIRF MEDICINES ARE ONLY INDICATED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN ADULT CANCER PATIENTS 18 YEARS OF AGE AND OLDER (16 YEARS OF AGE AND OLDER FOR ACTIQ® BRAND AND GENERIC EQUIVALENTS) WHO ARE ALREADY RECEIVING AND WHO ARE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY FOR THEIR UNDERLYING PERSISTENT CANCER PAIN.

Demonstrated Understanding	Prescribers N=302	
	N	%
0 correct responses	0	0.0
1 correct response	4	1.3
2 correct responses	5	1.7
3 correct responses	22	7.3
4 correct responses	46	15.2
5 correct responses	106	35.1
6 correct responses	119	39.4
Average number of correct responses	5.0	(4.8, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 7.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	4	1.5	0	0.0
2 correct responses	4	1.5	1	2.9
3 correct responses	19	7.1	3	8.6
4 correct responses	41	15.4	5	14.3
5 correct responses	91	34.1	15	42.9
6 correct responses	108	40.4	11	31.4
Average number of correct responses	5.0	(4.8, 6.0) [1]	4.9	(4.3, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	4	2.2	0	0.0	0	0.0	0	0.0
2 correct responses	3	1.6	0	0.0	2	3.0	0	0.0
3 correct responses	11	6.0	1	4.5	7	10.6	3	10.0
4 correct responses	27	14.8	6	27.3	9	13.6	3	10.0
5 correct responses	65	35.7	8	36.4	24	36.4	8	26.7
6 correct responses	72	39.6	7	31.8	24	36.4	16	53.3
Average number of correct responses	5.0	(4.7, 6.0) [1]	5.0	(4.2, 6.0) [1]	4.9	(4.5, 6.0) [1]	5.2	(4.5, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c >= 20 min N=75	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	1	2.1	2	1.2	1	1.3
2 correct responses	1	2.1	2	1.2	2	2.7
3 correct responses	4	8.5	10	6.0	8	10.7
4 correct responses	8	17.0	23	13.8	13	17.3
5 correct responses	14	29.8	65	38.9	20	26.7
6 correct responses	19	40.4	65	38.9	31	41.3
Average number of correct responses	4.9	(4.4, 6.0) [1]	5.0	(4.8, 6.0) [1]	4.9	(4.5, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=289		S-5b Telephone N=13	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	4	1.4	0	0.0
2 correct responses	5	1.7	0	0.0
3 correct responses	22	7.6	0	0.0
4 correct responses	44	15.2	2	15.4
5 correct responses	99	34.3	7	53.8
6 correct responses	115	39.8	4	30.8
Average number of correct responses	5.0	(4.8, 6.0) [1]	5.2	(4.1, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	2	1.9	2	1.7
2 correct responses	0	0.0	1	2.0	3	2.8	1	0.9
3 correct responses	1	3.6	5	10.2	6	5.7	10	8.5
4 correct responses	2	7.1	7	14.3	15	14.2	22	18.8
5 correct responses	12	42.9	15	30.6	40	37.7	38	32.5
6 correct responses	13	46.4	21	42.9	40	37.7	44	37.6
Average number of correct responses	5.3	(4.6, 6.0) [1]	5.0	(4.5, 6.0) [1]	5.0	(4.6, 6.0) [1]	4.9	(4.6, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 7.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #2

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	1	1.9	1	0.6	2	4.5	0	0.0
2 correct responses	1	1.9	2	1.2	1	2.3	0	0.0
3 correct responses	6	11.1	12	6.9	3	6.8	1	5.6
4 correct responses	2	3.7	31	17.9	7	15.9	2	11.1
5 correct responses	14	25.9	58	33.5	18	40.9	11	61.1
6 correct responses	30	55.6	69	39.9	13	29.5	4	22.2
Average number of correct responses	5.2	(4.7, 6.0) [1]	5.0	(4.7, 6.0) [1]	4.8	(4.2, 6.0) [1]	5.0	(4.1, 6.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [1]	299	99.0 (97.1, 99.8)
False	2	0.7
I don't know	1	0.3
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.		
8a: A personal history of psychiatric illness		
Yes [1]	250	82.8 (78.0, 86.9)
No	31	10.3
I don't know	21	7.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [1]	299	99.0 (97.1, 99.8)
No	2	0.7
I don't know	1	0.3

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True [1]	291	96.4 (93.6, 98.2)
False	9	3.0
I don't know	2	0.7

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 8.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	264	98.9 (96.8, 99.8)	35	100.0 (90.0, 100.0)
False	2	0.7	0	0.0
I don't know	1	0.4	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	227	85.0 (80.2, 89.1)	23	65.7 (47.8, 80.9)
No	24	9.0	7	20.0
I don't know	16	6.0	5	14.3

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	264	98.9 (96.8, 99.8)	35	100.0 (90.0, 100.0)
No	2	0.7	0	0.0
I don't know	1	0.4	0	0.0
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	258	96.6 (93.7, 98.4)	33	94.3 (80.8, 99.3)
False	9	3.4	0	0.0
I don't know	0	0.0	2	5.7

[1] Correct response

TABLE 8.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	181	99.5 (97.0, 100.0)	21	95.5 (77.2, 99.9)	66	100.0 (94.6, 100.0)	29	96.7 (82.8, 99.9)
False	1	0.5	1	4.5	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	0	0.0	1	3.3

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	153	84.1 (77.9, 89.1)	16	72.7 (49.8, 89.3)	52	78.8 (67.0, 87.9)	27	90.0 (73.5, 97.9)
No	16	8.8	5	22.7	9	13.6	1	3.3
I don't know	13	7.1	1	4.5	5	7.6	2	6.7
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	181	99.5 (97.0, 100.0)	21	95.5 (77.2, 99.9)	66	100.0 (94.6, 100.0)	29	96.7 (82.8, 99.9)
No	1	0.5	0	0.0	0	0.0	1	3.3
I don't know	0	0.0	1	4.5	0	0.0	0	0.0

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	175	96.2 (92.2, 98.4)	22	100.0 (84.6, 100.0)	64	97.0 (89.5, 99.6)	28	93.3 (77.9, 99.2)
False	6	3.3	0	0.0	1	1.5	2	6.7
I don't know	1	0.5	0	0.0	1	1.5	0	0.0

[1] Correct response

TABLE 8.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.						
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.						
True [1]	45	95.7 (85.5, 99.5)	166	99.4 (96.7, 100.0)	75	100.0 (95.2, 100.0)
False	1	2.1	1	0.6	0	0.0
I don't know	1	2.1	0	0.0	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.						
8a: A personal history of psychiatric illness						
Yes [1]	38	80.9 (66.7, 90.9)	142	85.0 (78.7, 90.1)	59	78.7 (67.7, 87.3)
No	4	8.5	16	9.6	9	12.0
I don't know	5	10.6	9	5.4	7	9.3

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse						
Yes [1]	47	100.0 (92.5, 100.0)	164	98.2 (94.8, 99.6)	75	100.0 (95.2, 100.0)
No	0	0.0	2	1.2	0	0.0
I don't know	0	0.0	1	0.6	0	0.0
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.						
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.						
True [1]	46	97.9 (88.7, 99.9)	161	96.4 (92.3, 98.7)	71	94.7 (86.9, 98.5)
False	1	2.1	5	3.0	3	4.0
I don't know	0	0.0	1	0.6	1	1.3

[1] Correct response

TABLE 8.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True [1]	286	99.0 (97.0, 99.8)	13	100.0 (75.3, 100.0)
False	2	0.7	0	0.0
I don't know	1	0.3	0	0.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.				
8a: A personal history of psychiatric illness				
Yes [1]	239	82.7 (77.8, 86.9)	11	84.6 (54.6, 98.1)
No	29	10.0	2	15.4
I don't know	21	7.3	0	0.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes [1]	286	99.0 (97.0, 99.8)	13	100.0 (75.3, 100.0)
No	2	0.7	0	0.0
I don't know	1	0.3	0	0.0

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True [1]	278	96.2 (93.3, 98.1)	13	100.0 (75.3, 100.0)
False	9	3.1	0	0.0
I don't know	2	0.7	0	0.0

[1] Correct response

TABLE 8.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.
SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	28	100.0 (87.7, 100.0)	47	95.9 (86.0, 99.5)	105	99.1 (94.9, 100.0)	117	100.0 (96.9, 100.0)
False	0	0.0	2	4.1	0	0.0	0	0.0
I don't know	0	0.0	0	0.0	1	0.9	0	0.0

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	22	78.6 (59.0, 91.7)	40	81.6 (68.0, 91.2)	88	83.0 (74.5, 89.6)	98	83.8 (75.8, 89.9)
No	2	7.1	6	12.2	11	10.4	12	10.3
I don't know	4	14.3	3	6.1	7	6.6	7	6.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	27	96.4 (81.7, 99.9)	48	98.0 (89.1, 99.9)	106	100.0 (96.6, 100.0)	116	99.1 (95.3,100.0)
No	1	3.6	0	0.0	0	0.0	1	0.9
I don't know	0	0.0	1	2.0	0	0.0	0	0.0
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	27	96.4 (81.7, 99.9)	49	100.0 (92.7, 100.0)	104	98.1 (93.4, 99.8)	109	93.2 (87.0, 97.0)
False	1	3.6	0	0.0	1	0.9	7	6.0
I don't know	0	0.0	0	0.0	1	0.9	1	0.9

[1] Correct response

TABLE 8.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS. SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 7: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.								
True [1]	53	98.1 (90.1, 100.0)	172	99.4 (96.8, 100.0)	44	100.0 (92.0, 100.0)	18	100.0 (81.5, 100.0)
False	1	1.9	0	0.0	0	0.0	0	0.0
I don't know	0	0.0	1	0.6	0	0.0	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 8: Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.								
8a: A personal history of psychiatric illness								
Yes [1]	43	79.6 (66.5, 89.4)	144	83.2 (76.8, 88.5)	39	88.6 (75.4, 96.2)	15	83.3 (58.6, 96.4)
No	4	7.4	19	11.0	3	6.8	3	16.7
I don't know	7	13.0	10	5.8	2	4.5	0	0.0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse								
Yes [1]	51	94.4 (84.6, 98.8)	173	100.0 (97.9, 100.0)	44	100.0 (92.0, 100.0)	18	100.0 (81.5, 100.0)
No	2	3.7	0	0.0	0	0.0	0	0.0
I don't know	1	1.9	0	0.0	0	0.0	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.								
True [1]	50	92.6 (82.1, 97.9)	168	97.1 (93.4, 99.1)	42	95.5 (84.5, 99.4)	18	100.0 (81.5, 100.0)
False	3	5.6	4	2.3	2	4.5	0	0.0
I don't know	1	1.9	1	0.6	0	0.0	0	0.0

[1] Correct response

TABLE 8.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 3: TIRF MEDICINES CONTAIN FENTANYL, AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE, WITH ABUSE LIABILITY SIMILAR TO OTHER OPIOID ANALGESICS.

Demonstrated Understanding	Eligible and Complete Respondents N=302	
	N	%
0 correct responses	0	0.0
1 correct response	0	0.0
2 correct responses	8	2.6
3 correct responses	53	17.5
4 correct responses	241	79.8
Average number of correct responses	3.8	(3.6, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 8.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	7	2.6	1	2.9
3 correct responses	41	15.4	12	34.3
4 correct responses	219	82.0	22	62.9
Average number of correct responses	3.8	(3.6, 4.0) [1]	3.6	(3.0, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	2	1.1	1	4.5	2	3.0	3	10.0
3 correct responses	34	18.7	6	27.3	12	18.2	1	3.3
4 correct responses	146	80.2	15	68.2	52	78.8	26	86.7
Average number of correct responses	3.8	(3.6, 4.0) [1]	3.6	(3.0, 4.0) [1]	3.8	(3.4, 4.0) [1]	3.8	(3.2, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0
2 correct responses	2	4.3	4	2.4	2	2.7
3 correct responses	8	17.0	27	16.2	16	21.3
4 correct responses	37	78.7	136	81.4	57	76.0
Average number of correct responses	3.7	(3.3, 4.0) [1]	3.8	(3.5, 4.0) [1]	3.7	(3.4, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=289		S-5b Telephone N=13	
	N	%	N	%
0 correct responses	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0
2 correct responses	8	2.8	0	0.0
3 correct responses	51	17.6	2	15.4
4 correct responses	230	79.6	11	84.6
Average number of correct responses	3.8	(3.6, 4.0) [1]	3.8	(3.0, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	1	3.6	2	4.1	2	1.9	3	2.6
3 correct responses	6	21.4	8	16.3	17	16.0	22	18.8
4 correct responses	21	75.0	39	79.6	87	82.1	92	78.6
Average number of correct responses	3.7	(3.1, 4.0) [1]	3.8	(3.3, 4.0) [1]	3.8	(3.5, 4.0) [1]	3.8	(3.5, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 8.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #3

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	0	0.0
1 correct response	0	0.0	0	0.0	0	0.0	0	0.0
2 correct responses	4	7.4	2	1.2	1	2.3	0	0.0
3 correct responses	11	20.4	31	17.9	5	11.4	3	16.7
4 correct responses	39	72.2	140	80.9	38	86.4	15	83.3
Average number of correct responses	3.6	(3.2, 4.0) [1]	3.8	(3.6, 4.0) [1]	3.8	(3.4, 4.0) [1]	3.8	(3.1, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
False [1]	279	92.4 (88.8, 95.1)
True	16	5.3
I don't know	7	2.3
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True [1]	286	94.7 (91.5, 96.9)
False	7	2.3
I don't know	9	3.0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True [1]	274	90.7 (86.9, 93.8)
False	16	5.3
I don't know	12	4.0

Question	Eligible and Complete Respondents N=302	
	N	% (95% CI) [2]
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	225	74.5 (69.2, 79.3)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	6	2.0
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25	8.3
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	34	11.3
I don't know	12	4.0

[1] Correct response
[2] All confidence intervals are exact binomial 95% confidence intervals.

TABLE 9.1.1 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	246	92.1 (88.2, 95.1)	33	94.3 (80.8, 99.3)
True	16	6.0	0	0.0
I don't know	5	1.9	2	5.7
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	254	95.1 (91.8, 97.4)	32	91.4 (76.9, 98.2)
False	7	2.6	0	0.0
I don't know	6	2.2	3	8.6

Question	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	% (95% CI)	N	% (95% CI)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	245	91.8 (87.8, 94.8)	29	82.9 (66.4, 93.4)
False	13	4.9	3	8.6
I don't know	9	3.4	3	8.6
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.				
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	197	73.8 (68.1, 79.0)	28	80.0 (63.1, 91.6)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	6	2.2	0	0.0
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	23	8.6	2	5.7
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	29	10.9	5	14.3
I don't know	12	4.5	0	0.0

[1] Correct response

TABLE 9.1.2 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	167	91.8 (86.8, 95.3)	20	90.9 (70.8, 98.9)	61	92.4 (83.2, 97.5)	29	96.7 (82.8, 99.9)
True	11	6.0	1	4.5	3	4.5	1	3.3
I don't know	4	2.2	1	4.5	2	3.0	0	0.0

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	175	96.2 (92.2, 98.4)	20	90.9 (70.8, 98.9)	61	92.4 (83.2, 97.5)	28	93.3 (77.9, 99.2)
False	2	1.1	2	9.1	2	3.0	1	3.3
I don't know	5	2.7	0	0.0	3	4.5	1	3.3
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	169	92.9 (88.1, 96.1)	20	90.9 (70.8, 98.9)	55	83.3 (72.1, 91.4)	28	93.3 (77.9, 99.2)
False	8	4.4	1	4.5	7	10.6	0	0.0
I don't know	5	2.7	1	4.5	4	6.1	2	6.7

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.								
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	133	73.1 (66.0, 79.4)	14	63.6 (40.7, 82.8)	52	78.8 (67.0, 87.9)	25	83.3 (65.3, 94.4)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	4	2.2	1	4.5	0	0.0	1	3.3
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	21	11.5	2	9.1	1	1.5	1	3.3

Question	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	20	11.0	1	4.5	10	15.2	2	6.7
I don't know	4	2.2	4	18.2	3	4.5	1	3.3

[1] Correct response

TABLE 9.1.3 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.						
10b: TIRF medicines are interchangeable with each other regardless of route of administration.						
False [1]	44	93.6 (82.5, 98.7)	156	93.4 (88.5, 96.7)	67	89.3 (80.1, 95.3)
True	2	4.3	8	4.8	5	6.7
I don't know	1	2.1	3	1.8	3	4.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.						
True [1]	45	95.7 (85.5, 99.5)	157	94.0 (89.3, 97.1)	73	97.3 (90.7, 99.7)
False	2	4.3	5	3.0	0	0.0
I don't know	0	0.0	5	3.0	2	2.7
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.						
True [1]	43	91.5 (79.6, 97.6)	154	92.2 (87.1, 95.8)	67	89.3 (80.1, 95.3)
False	2	4.3	5	3.0	7	9.3
I don't know	2	4.3	8	4.8	1	1.3

Question	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.						
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	27	57.4 (42.2, 71.7)	129	77.2 (70.1, 83.4)	59	78.7 (67.7, 87.3)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	0.0	3	1.8	2	2.7
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	5	10.6	13	7.8	6	8.0
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	13	27.7	14	8.4	6	8.0
I don't know	2	4.3	8	4.8	2	2.7

[1] Correct response

TABLE 9.1.5 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a - Internet**
- **S-5b - Telephone**

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
False [1]	267	92.4 (88.7, 95.2)	12	92.3 (64.0, 99.8)
True	15	5.2	1	7.7
I don't know	7	2.4	0	0.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True [1]	275	95.2 (92.0, 97.3)	11	84.6 (54.6, 98.1)
False	7	2.4	0	0.0
I don't know	7	2.4	2	15.4
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True [1]	264	91.3 (87.5, 94.3)	10	76.9 (46.2, 95.0)
False	14	4.8	2	15.4
I don't know	11	3.8	1	7.7

Question	S-5a Internet N=289		S-5b Telephone N=13	
	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.				
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	215	74.4 (69.0, 79.3)	10	76.9 (46.2, 95.0)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	5	1.7	1	7.7
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	24	8.3	1	7.7
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	33	11.4	1	7.7
I don't know	12	4.2	0	0.0

[1] Correct response

TABLE 9.1.6 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	26	92.9 (76.5, 99.1)	47	95.9 (86.0, 99.5)	98	92.5 (85.7, 96.7)	106	90.6 (83.8, 95.2)
True	1	3.6	0	0.0	7	6.6	8	6.8
I don't know	1	3.6	2	4.1	1	0.9	3	2.6

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	28	100.0 (87.7, 100.0)	43	87.8 (75.2, 95.4)	102	96.2 (90.6, 99.0)	111	94.9 (89.2, 98.1)
False	0	0.0	2	4.1	2	1.9	3	2.6
I don't know	0	0.0	4	8.2	2	1.9	3	2.6
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	25	89.3 (71.8, 97.7)	39	79.6 (65.7, 89.8)	100	94.3 (88.1, 97.9)	108	92.3 (85.9, 96.4)
False	0	0.0	7	14.3	4	3.8	5	4.3
I don't know	3	10.7	3	6.1	2	1.9	4	3.4

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.								
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	20	71.4 (51.3, 86.8)	36	73.5 (58.9, 85.1)	76	71.7 (62.1, 80.0)	91	77.8 (69.2, 84.9)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	0.0	2	4.1	1	0.9	3	2.6
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	1	3.6	1	2.0	10	9.4	13	11.1

Question	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	5	17.9	8	16.3	15	14.2	6	5.1
I don't know	2	7.1	2	4.1	4	3.8	4	3.4

[1] Correct response

TABLE 9.1.7 PRIMARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 10: Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.								
10b: TIRF medicines are interchangeable with each other regardless of route of administration.								
False [1]	53	98.1 (90.1, 100.0)	157	90.8 (85.4, 94.6)	40	90.9 (78.3, 97.5)	17	94.4 (72.7, 99.9)
True	1	1.9	10	5.8	4	9.1	0	0.0
I don't know	0	0.0	6	3.5	0	0.0	1	5.6

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.								
True [1]	50	92.6 (82.1, 97.9)	165	95.4 (91.1, 98.0)	42	95.5 (84.5, 99.4)	16	88.9 (65.3, 98.6)
False	3	5.6	3	1.7	1	2.3	0	0.0
I don't know	1	1.9	5	2.9	1	2.3	2	11.1
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.								
True [1]	45	83.3 (70.7, 92.1)	162	93.6 (88.9, 96.8)	41	93.2 (81.3, 98.6)	16	88.9 (65.3, 98.6)
False	5	9.3	5	2.9	3	6.8	2	11.1
I don't know	4	7.4	6	3.5	0	0.0	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Question 14: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.								
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [1]	43	79.6 (66.5, 89.4)	128	74.0 (66.8, 80.4)	33	75.0 (59.7, 86.8)	15	83.3 (58.6, 96.4)
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	2	3.7	2	1.2	1	2.3	1	5.6
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	3	5.6	13	7.5	4	9.1	0	0.0

Question	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	3	5.6	22	12.7	5	11.4	2	11.1
I don't know	3	5.6	8	4.6	1	2.3	0	0.0

[1] Correct response

TABLE 9.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 4: TIRF MEDICINES ARE NOT INTERCHANGEABLE WITH EACH OTHER, REGARDLESS OF ROUTE OF ADMINISTRATION.

Demonstrated Understanding	Eligible and Complete Respondents N=302	
	N	%
0 correct responses	1	0.3
1 correct response	3	1.0
2 correct responses	28	9.3
3 correct responses	75	24.8
4 correct responses	195	64.6
Average number of correct responses	3.5	(3.3, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution

TABLE 9.2.1 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 1: READING MEDICATION GUIDE OR FULL PRESCRIBING INFORMATION (QUESTIONS 20, 21, 22 AND 23):

- **S-1a - Respondents who received and read the Full Prescribing Information for the TIRF medicine that they prescribe, or who received and read the Medication Guide.**
- **S-1b - Respondents who did not receive or did not read the Full Prescribing Information for the TIRF medication that they prescribe (answered "No" or "I don't know" to Question 21) and did not receive or did not read the Medication Guide for the TIRF medicine that they prescribe (answered "No" or "I don't know" to Question 23).**

Demonstrated Understanding	S-1a Read Medication Guide or Prescribing Info N=267		S-1b Did not read Medication Guide or Prescribing Info N=35	
	N	%	N	%
0 correct responses	1	0.4	0	0.0
1 correct response	2	0.7	1	2.9
2 correct responses	25	9.4	3	8.6
3 correct responses	66	24.7	9	25.7
4 correct responses	173	64.8	22	62.9
Average number of correct responses	3.5	(3.3, 4.0) [1]	3.5	(3.0, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.2.2 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 2: MEDICAL DEGREE OF RESPONDENTS (QUESTION 32):

- **S-2a - MD**
- **S-2b – DO**
- **S-2c – Nurse Practitioner**
- **S-2d - Physician Assistant**

Demonstrated Understanding	S-2a MD N=182		S-2b DO N=22		S-2c Nurse Practitioner N=66		S-2d Physician Assistant N=30	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	1	1.5	0	0.0
1 correct response	3	1.6	0	0.0	0	0.0	0	0.0
2 correct responses	15	8.2	4	18.2	6	9.1	3	10.0
3 correct responses	45	24.7	6	27.3	19	28.8	4	13.3
4 correct responses	119	65.4	12	54.5	40	60.6	23	76.7
Average number of correct responses	3.5	(3.3, 4.0) [1]	3.4	(2.7, 4.0) [1]	3.5	(3.1, 4.0) [1]	3.7	(3.1, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.2.3 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 3: TIME TO COMPLETE SURVEY – INTERNET:

- **S-3a - <10 min**
- **S-3b – 10 to <20 min**
- **S-3c – ≥ 20 min**

Demonstrated Understanding	S-3a <10 min N=47		S-3b 10 to <20 min N=167		S-3c ≥ 20 min N=75	
	N	%	N	%	N	%
0 correct responses	0	0.0	1	0.6	0	0.0
1 correct response	0	0.0	1	0.6	0	0.0
2 correct responses	7	14.9	12	7.2	8	10.7
3 correct responses	15	31.9	41	24.6	18	24.0
4 correct responses	25	53.2	112	67.1	49	65.3
Average number of correct responses	3.4	(2.9, 4.0) [1]	3.6	(3.3, 4.0) [1]	3.5	(3.2, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.2.5 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 5: MODALITY TO COMPLETE SURVEY:

- **S-5a – Internet**
- **S-5b - Telephone**

Demonstrated Understanding	S-5a Internet N=289		S-5b Telephone N=13	
	N	%	N	%
0 correct responses	1	0.3	0	0.0
1 correct response	1	0.3	2	15.4
2 correct responses	27	9.3	1	7.7
3 correct responses	74	25.6	1	7.7
4 correct responses	186	64.4	9	69.2
Average number of correct responses	3.5	(3.4, 4.0) [1]	3.3	(2.5, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.2.6 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 6: TIME PRACTICING MEDICINE (QUESTION 33):

- **S-6a - Less than 3 years**
- **S-6b - 3 to 5 years**
- **S-6c - 6 to 15 years**
- **S-6d - More than 15 years**

Demonstrated Understanding	S-6a Less than 3 years N=28		S-6b 3 to 5 years N=49		S-6c 6 to 15 years N=106		S-6d More than 15 years N=117	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	0	0.0	0	0.0	1	0.9
1 correct response	0	0.0	3	6.1	0	0.0	0	0.0
2 correct responses	1	3.6	6	12.2	11	10.4	10	8.5
3 correct responses	11	39.3	10	20.4	26	24.5	28	23.9
4 correct responses	16	57.1	30	61.2	69	65.1	78	66.7
Average number of correct responses	3.5	(3.0, 4.0) [1]	3.4	(2.9, 4.0) [1]	3.5	(3.2, 4.0) [1]	3.6	(3.3, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

TABLE 9.2.7 SECONDARY ANALYSIS OF RESPONSES TO QUESTIONS LINKED TO KEY RISK MESSAGE #4

KEY RISK MESSAGE 1: TIRF MEDICINES ARE CONTRAINDICATED IN OPIOID NON-TOLERANT PATIENTS.

SUB-GROUP ANALYSIS 7: NUMBER OF TIMES PER MONTHS PRESCRIBING TIRF MEDICINES WITHIN THE LAST 6 MONTHS (QUESTION 29):

- **S-7a - None**
- **S-7b - 1-2 times a month**
- **S-7c - 3 - 5 times a month**
- **S-7d - More than 5 times a month**

Demonstrated Understanding	S-7a None N=54		S-7b 1-2 times a month N=173		S-7c 3 - 5 times a month N=44		S-7d More than 5 times a month N=18	
	N	%	N	%	N	%	N	%
0 correct responses	0	0.0	1	0.6	0	0.0	0	0.0
1 correct response	1	1.9	0	0.0	0	0.0	2	11.1
2 correct responses	6	11.1	14	8.1	5	11.4	1	5.6
3 correct responses	10	18.5	48	27.7	10	22.7	0	0.0
4 correct responses	37	68.5	110	63.6	29	65.9	15	83.3
Average number of correct responses	3.5	(3.1, 4.0) [1]	3.5	(3.3, 4.0) [1]	3.5	(3.1, 4.0) [1]	3.6	(2.8, 4.0) [1]

[1] One-sided 95 % confidence interval using the normal approximation to the Poisson distribution.

Appendix C Findings Report: Qualitative Research to Evaluate the Prescriber and Pharmacist 12-month REMS Assessment Surveys for TIRF Medicines

Findings Report:
Qualitative Research to Evaluate the Prescriber and Pharmacist 12-month REMS Assessment Surveys for Transmucosal Immediate Release Fentanyl (TIRF) Medicines

UBC Contacts:
Megan Leone-Perkins, PhD, Research Lead
Blythe Vito, Senior Manager
215-390-1385

16 December 2013
Version 3.0

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1 INTRODUCTION

The Food and Drug Administration (FDA) has approved a shared risk evaluation and mitigation strategy (REMS) for the class of transmucosal immediate-release fentanyl (TIRF) products. The products in the TIRF REMS Program include ABSTRAL® (fentanyl) sublingual tablets CII, ACTIQ® (fentanyl citrate) oral transmucosal lozenge CII, FENTORA® (fentanyl buccal tablet) CII, LAZANDA® (fentanyl) nasal spray CII, and ONSOLIS® (fentanyl buccal soluble film) CII, SUBSYS® (fentanyl) sublingual spray CII, as well as generic forms of the aforementioned products.

The FDA provided feedback to the TIRF REMS Industry Group (TRIG) on the Knowledge, Attitude, and Behavior survey results for prescribers and pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions. The research undertaken included review of the questions identified by the FDA that had low correct response rates, as well as two new questions approved by the TRIG. This document describes how this research was conducted, including a description of research participants, and major findings used to inform KAB survey revisions.

2 RESEARCH OBJECTIVES

The purpose of this qualitative research was to investigate the causes for low correct response rates to specific prescriber and pharmacist questions used in the survey administered as part of the TIRF REMS Access Program 12-month REMS Assessment. Additionally, this research was conducted to assess proposed revised wording to select questions, as well as to assess comprehension of two additional questions.

The questions reviewed during the qualitative research interviews included the following (see Appendix A for full question sets. Readers should note that the survey content that is displayed in blue font represents proposed revised wording.):

- Prescribers reviewed:
  - 10 items from the Prescriber 12-month REMS Assessment Survey Questions: 5a, 5c, 8e, 11b, 12c, 12d, 15a-d
  - New questions 7 and 19
- Pharmacists reviewed:
  - 7 items from the Pharmacist 12-month REMS Assessment Survey Questions: 5a, 5c, 8 (a-e);
  - New question 7

The objectives of this research were to:

- Evaluate clarity and comprehension of questions and answer options used in the 12-month assessment;
- Identify terms, questions or topics for clarification or revision based on any areas of confusion with or misunderstanding for current wording;
- Determine how participants understand specific questions and why those questions are answered a particular way;
- Determine how certain questions might be understood differently and answered more accurately if further clarified;
- Evaluate alternative language for these questions.

3 RESEARCH DESIGN

3.1 OVERVIEW

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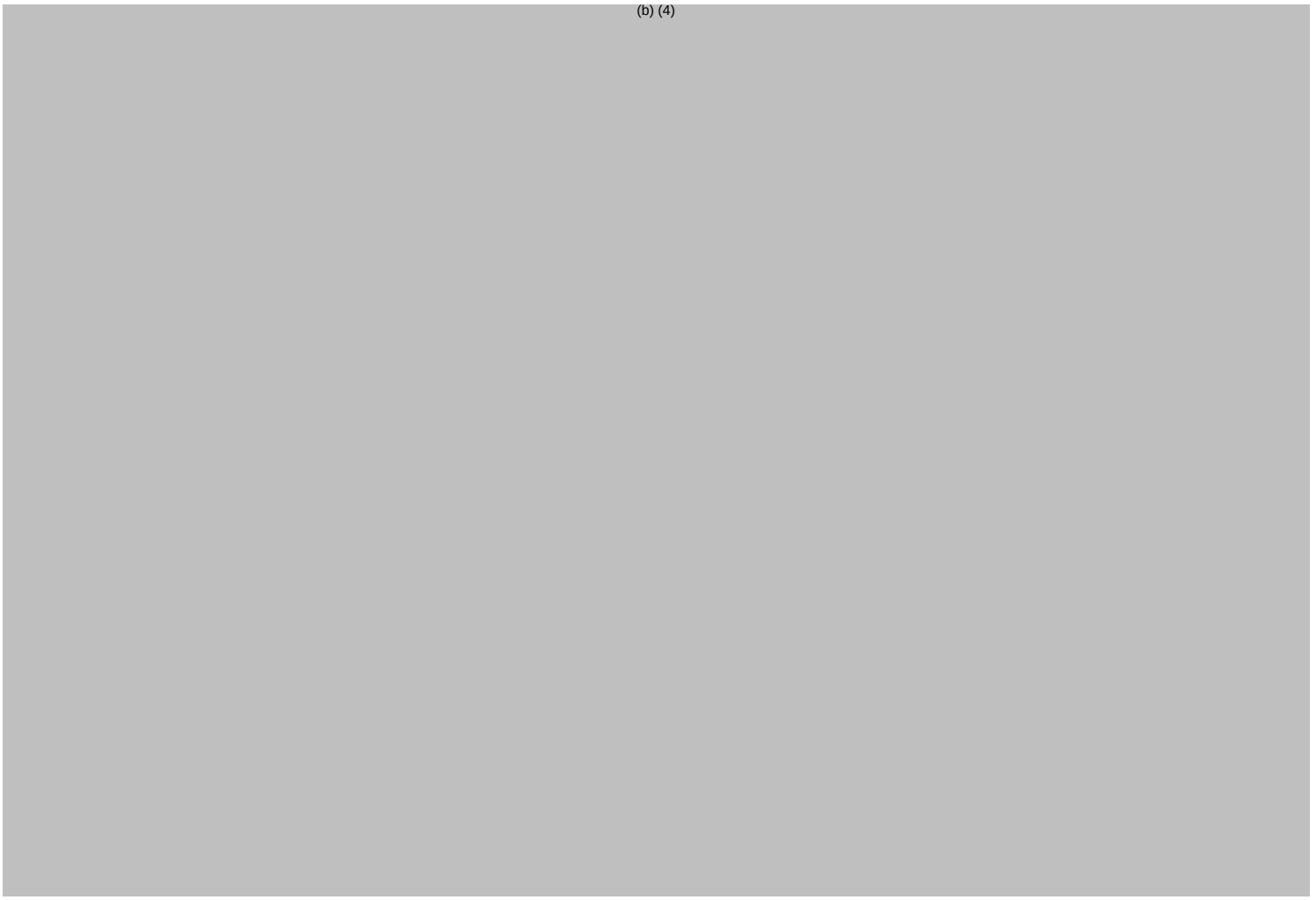

3.2 ELIGIBILITY CRITERIA

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3.3 RECRUITMENT

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3.4 PARTICIPANT DEMOGRAPHICS

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4 INTERVIEW DESIGN

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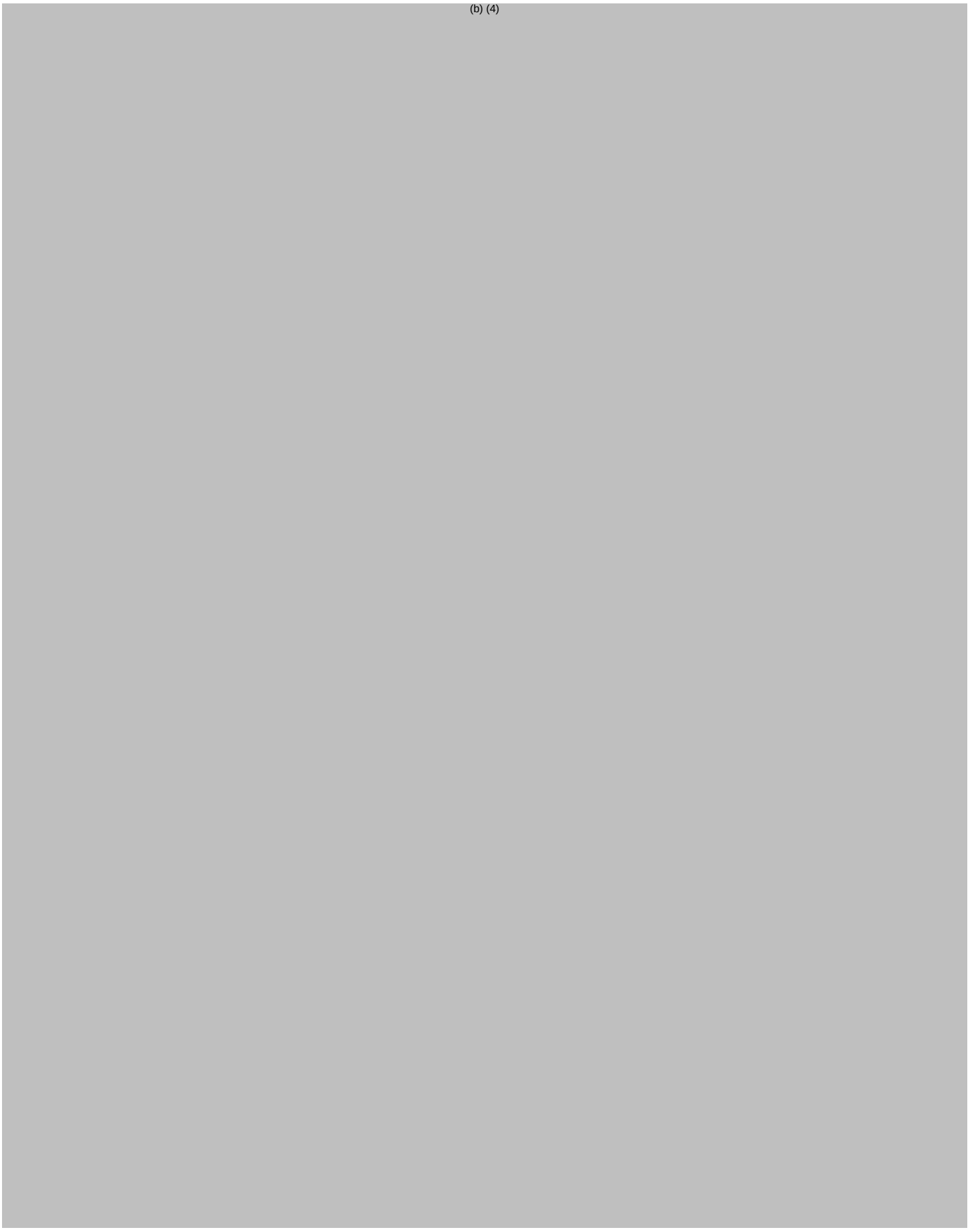

5 RESEARCH FINDINGS

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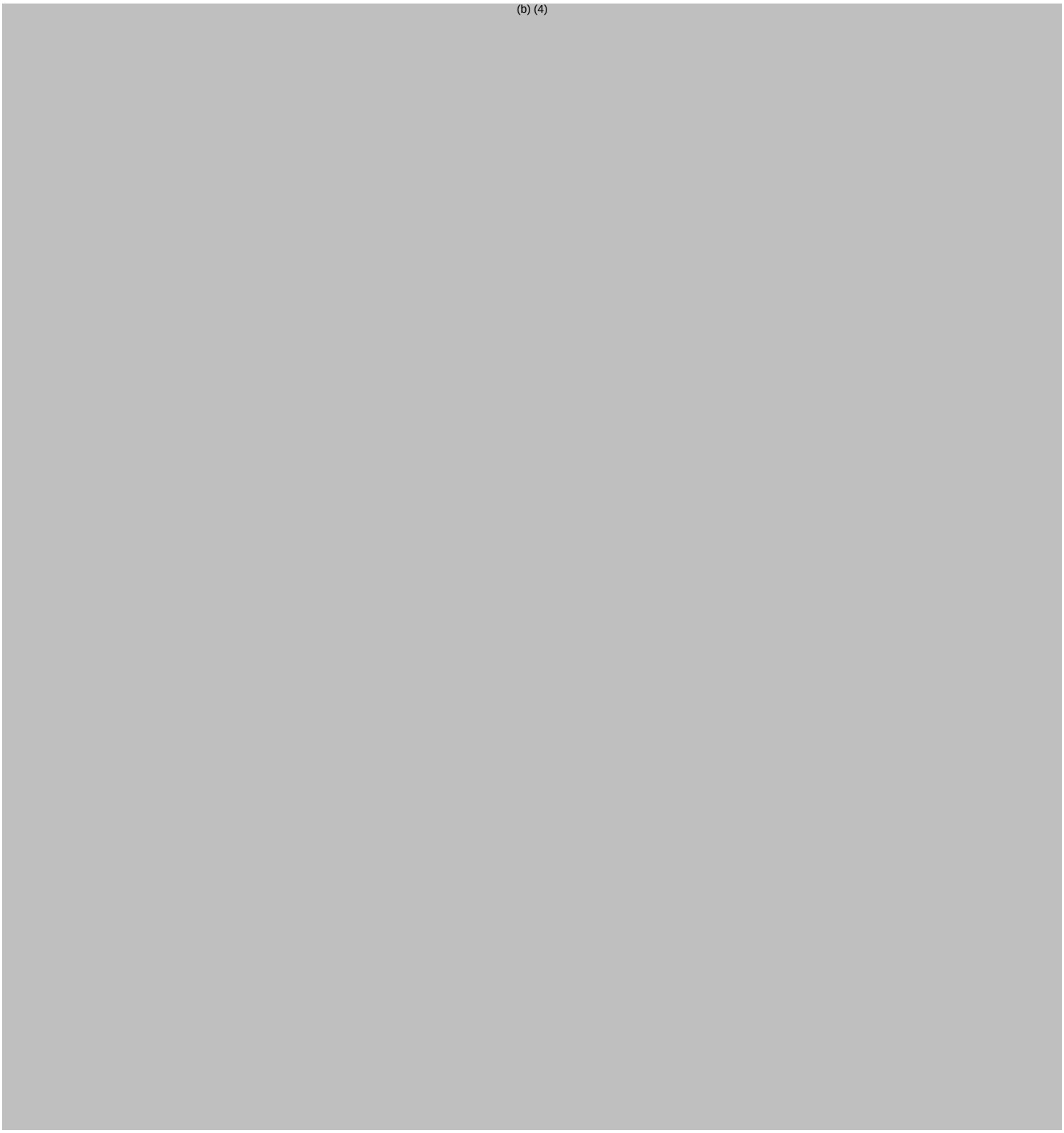

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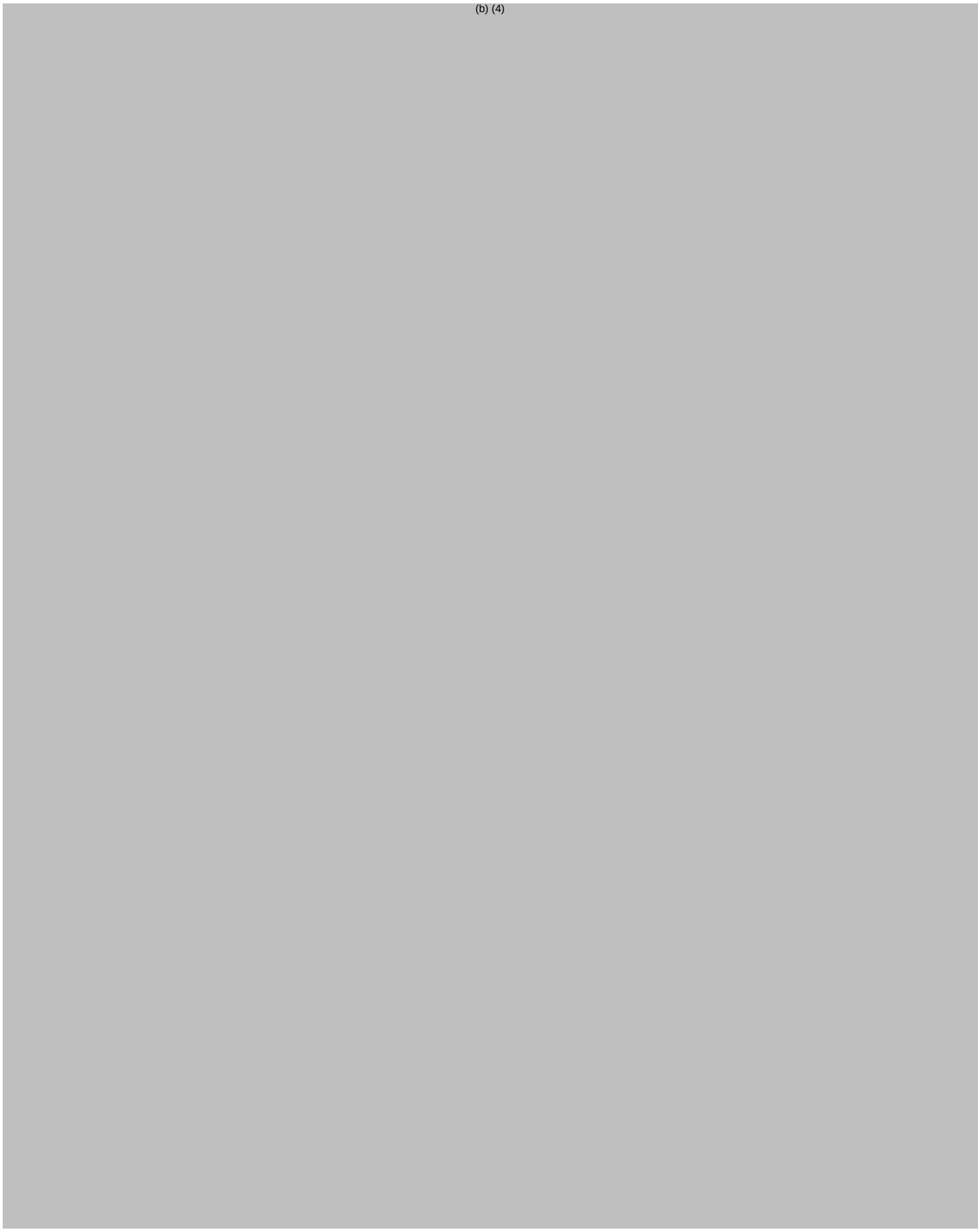

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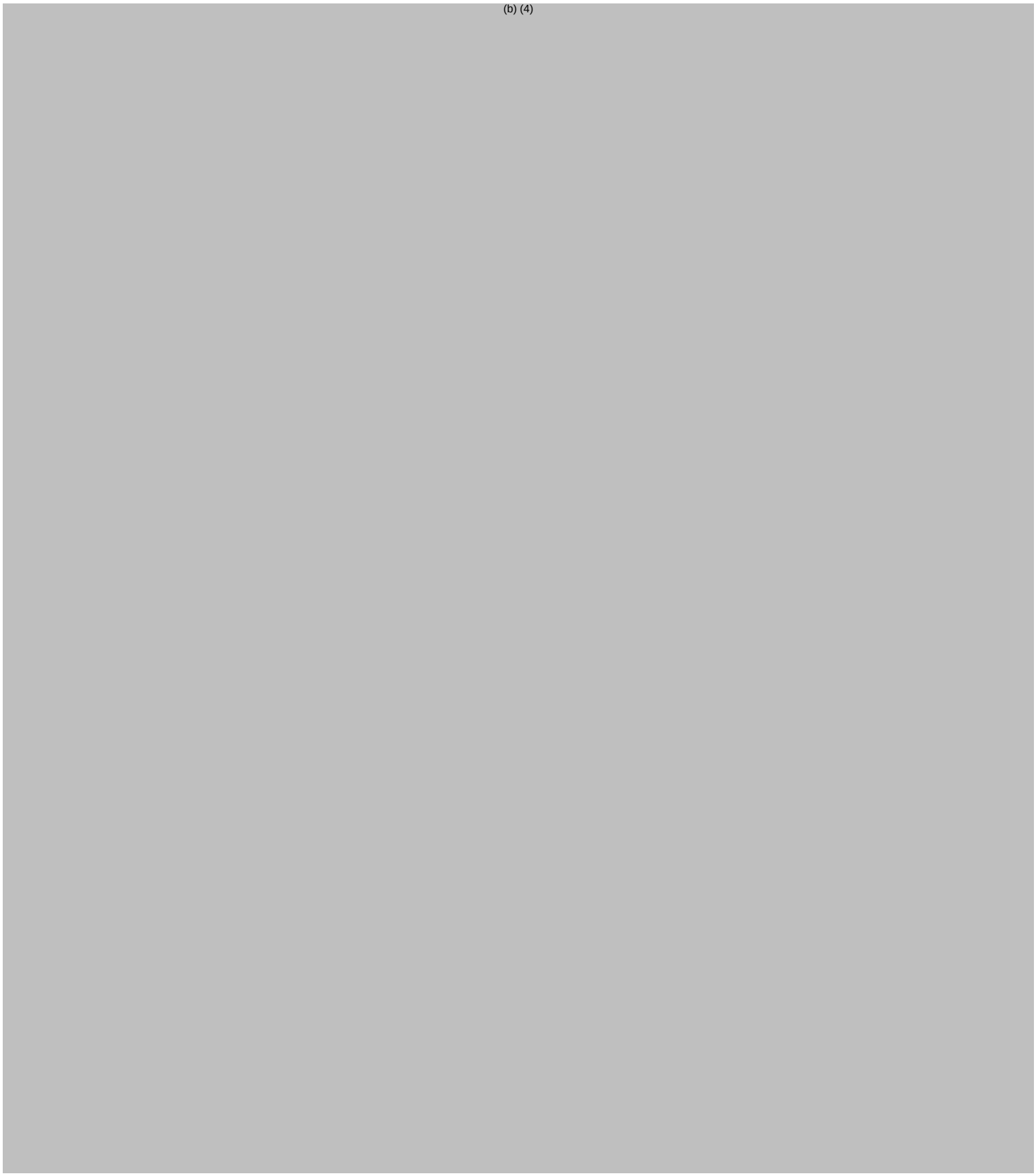

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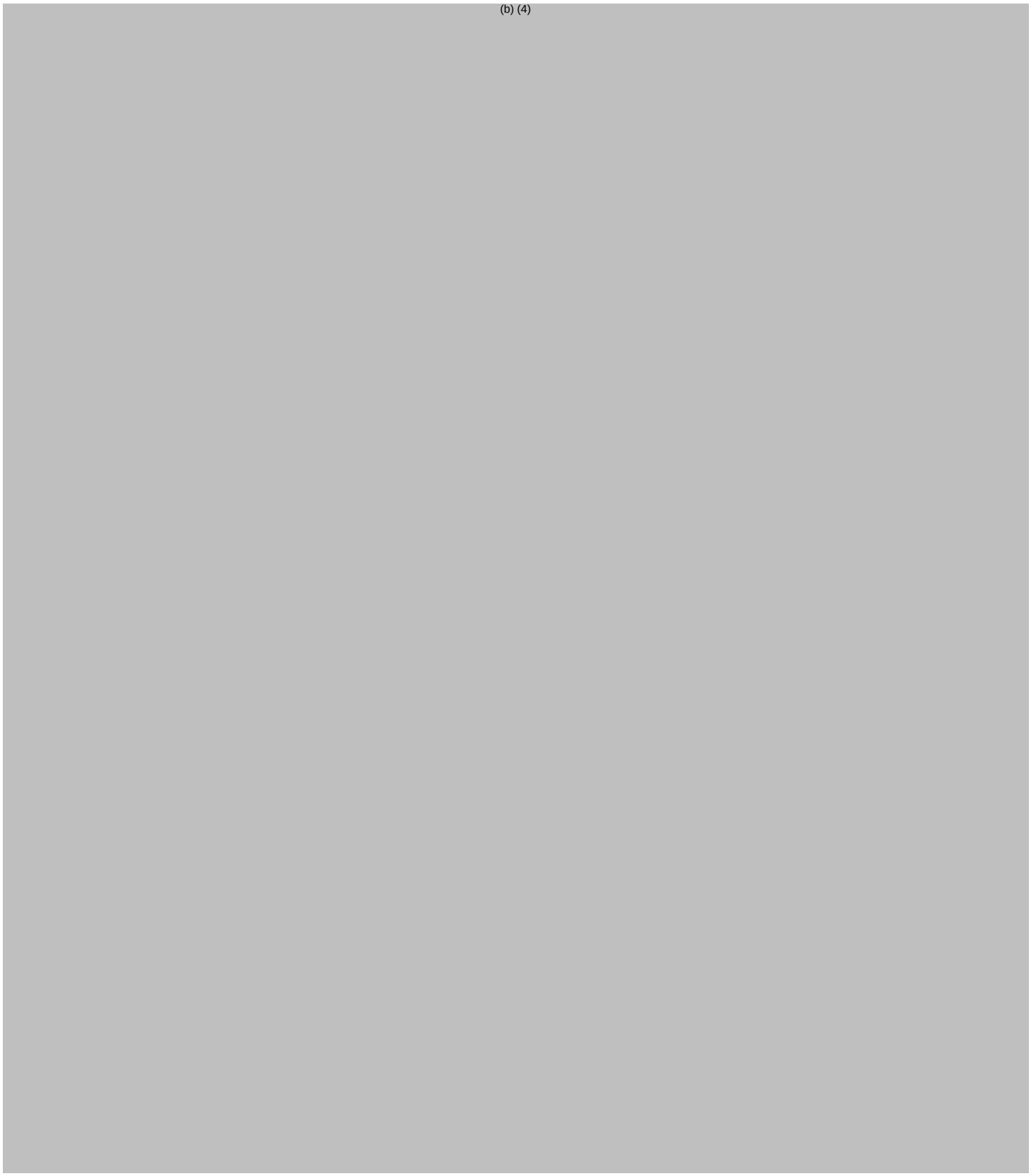

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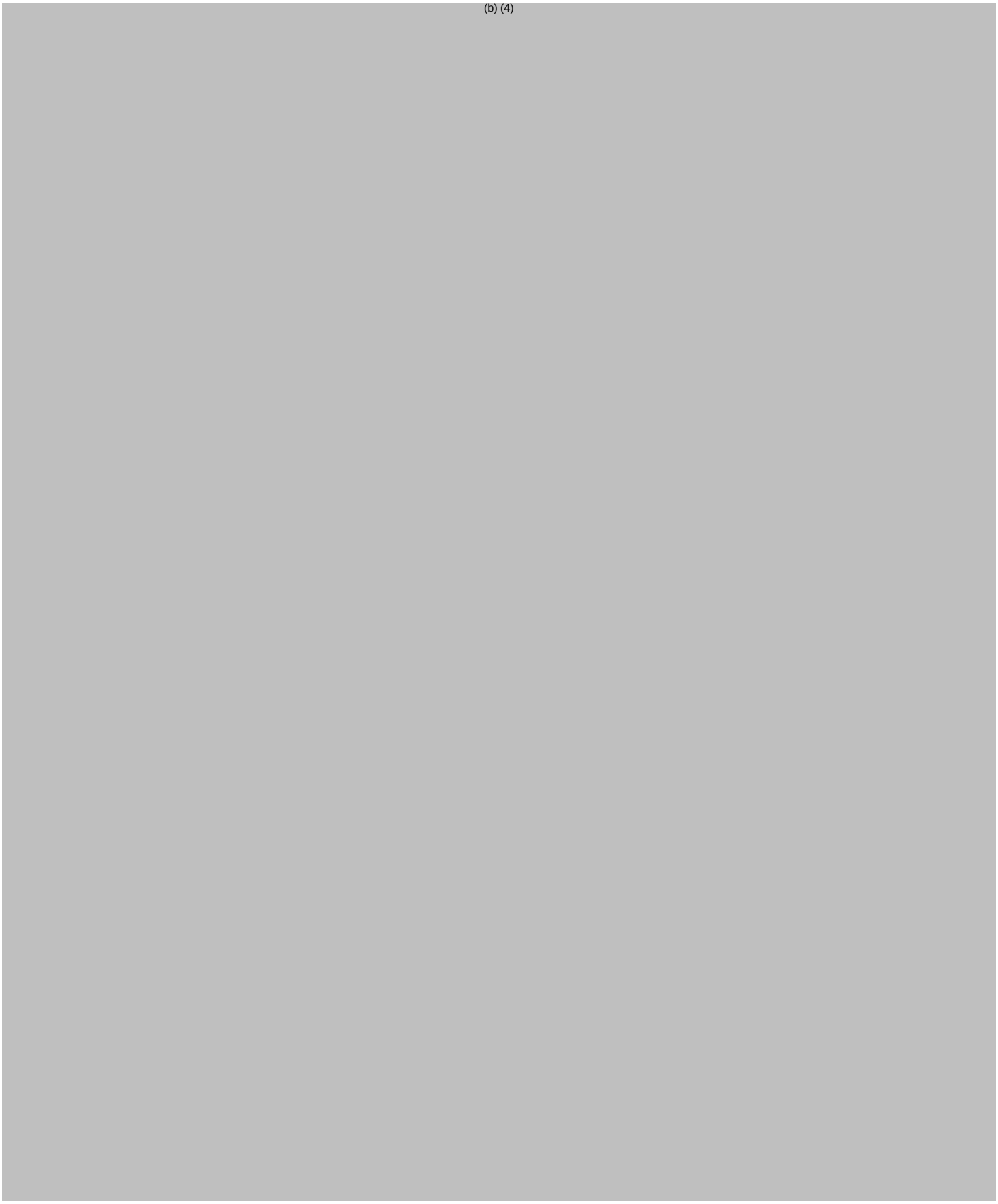

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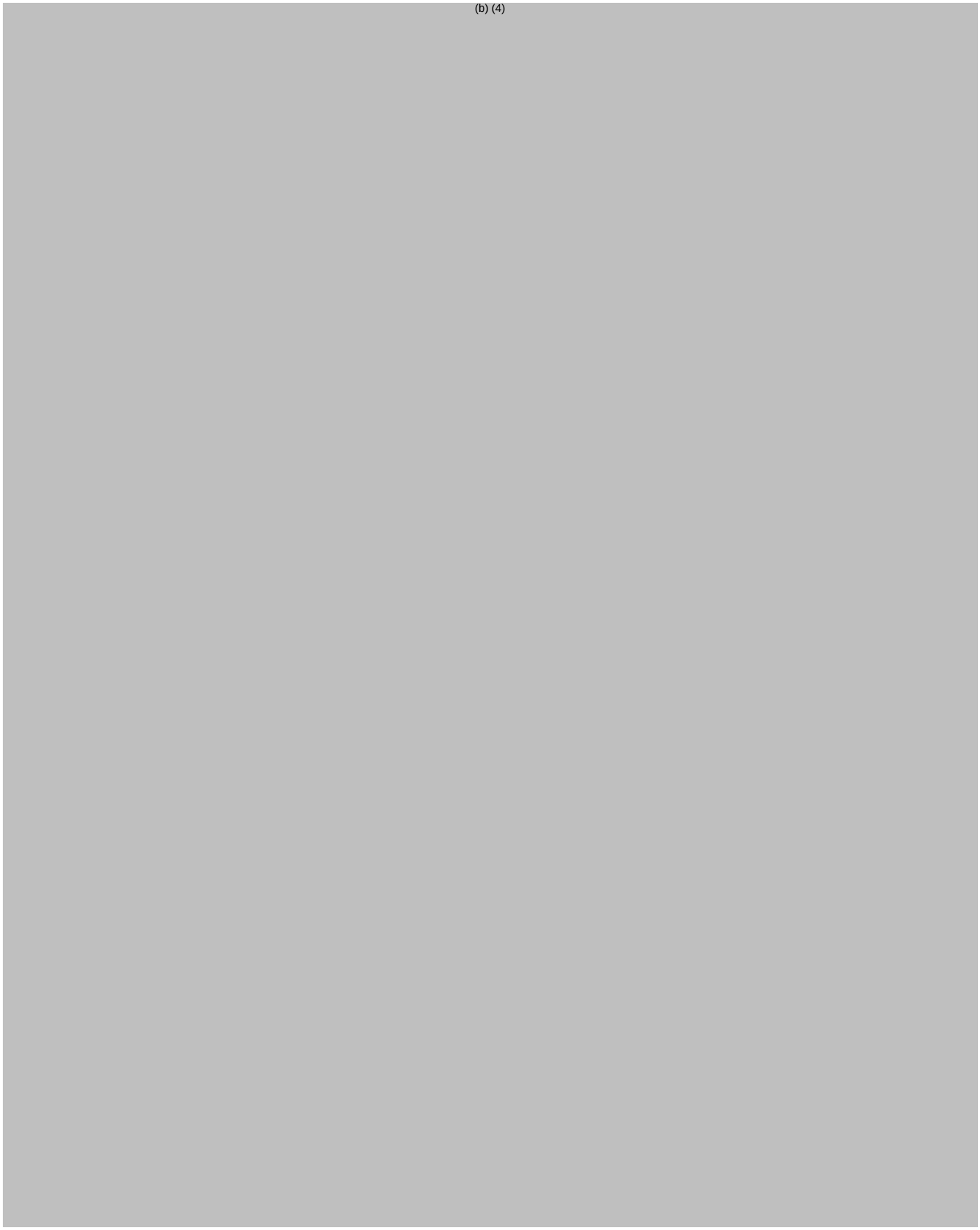

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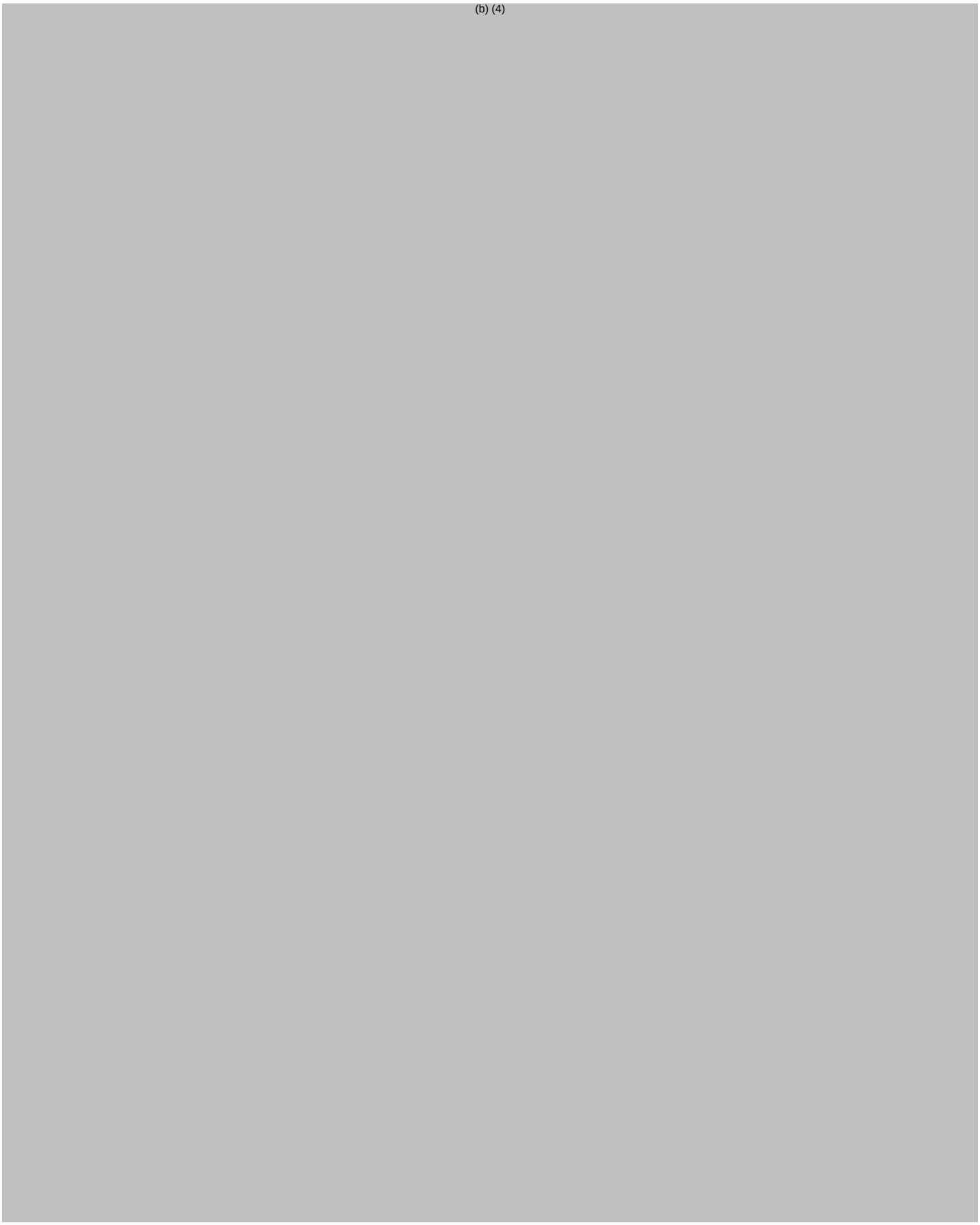

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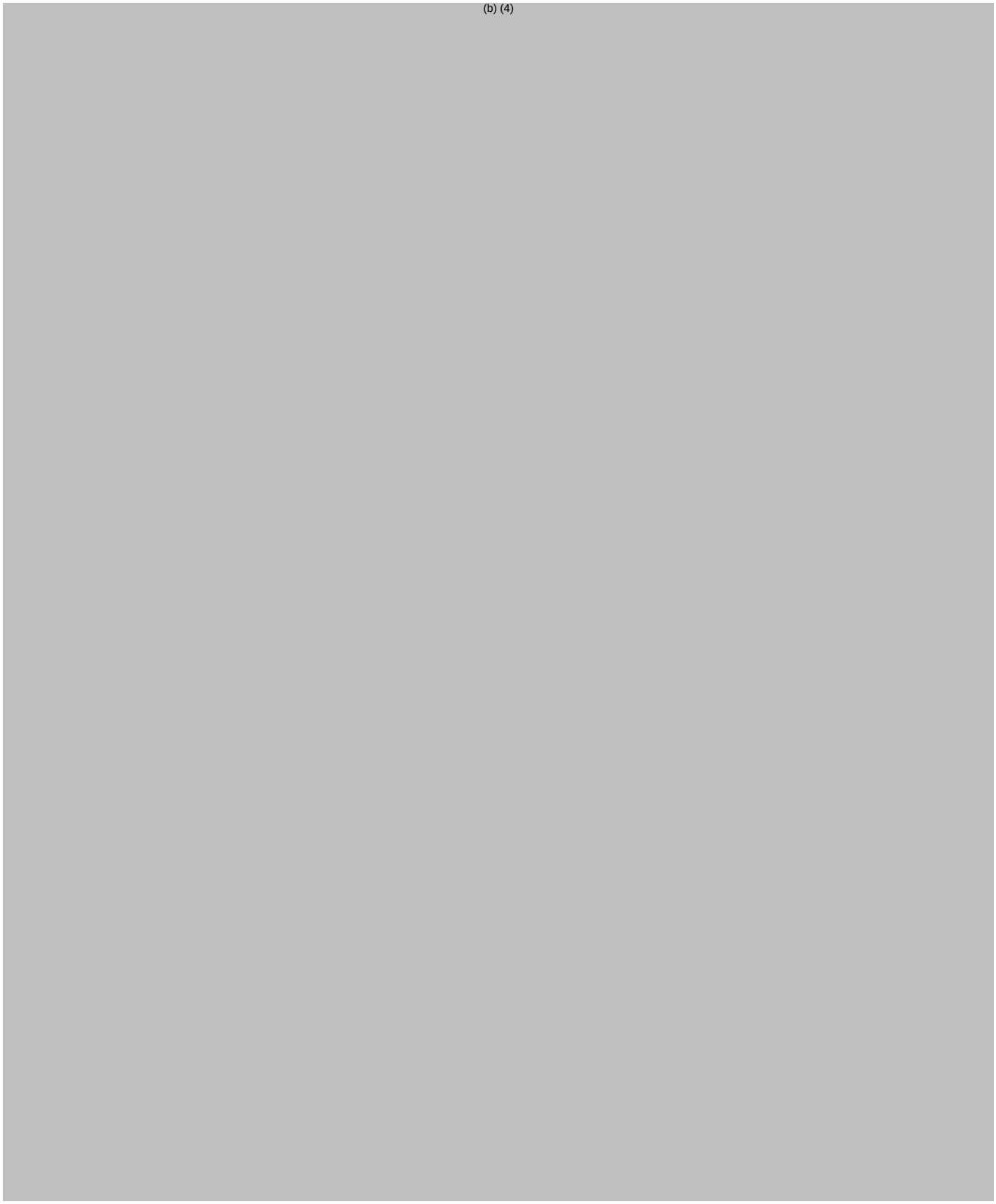

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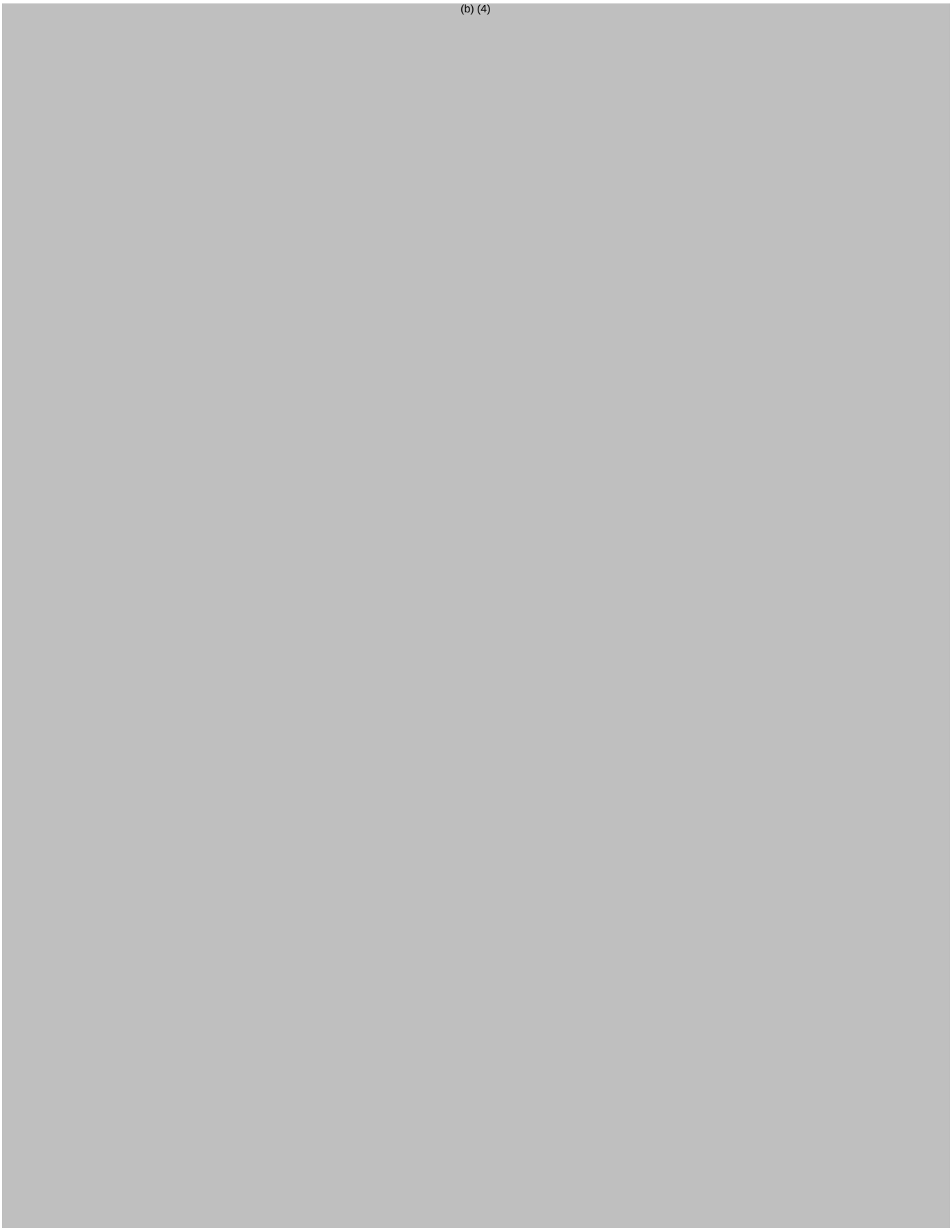

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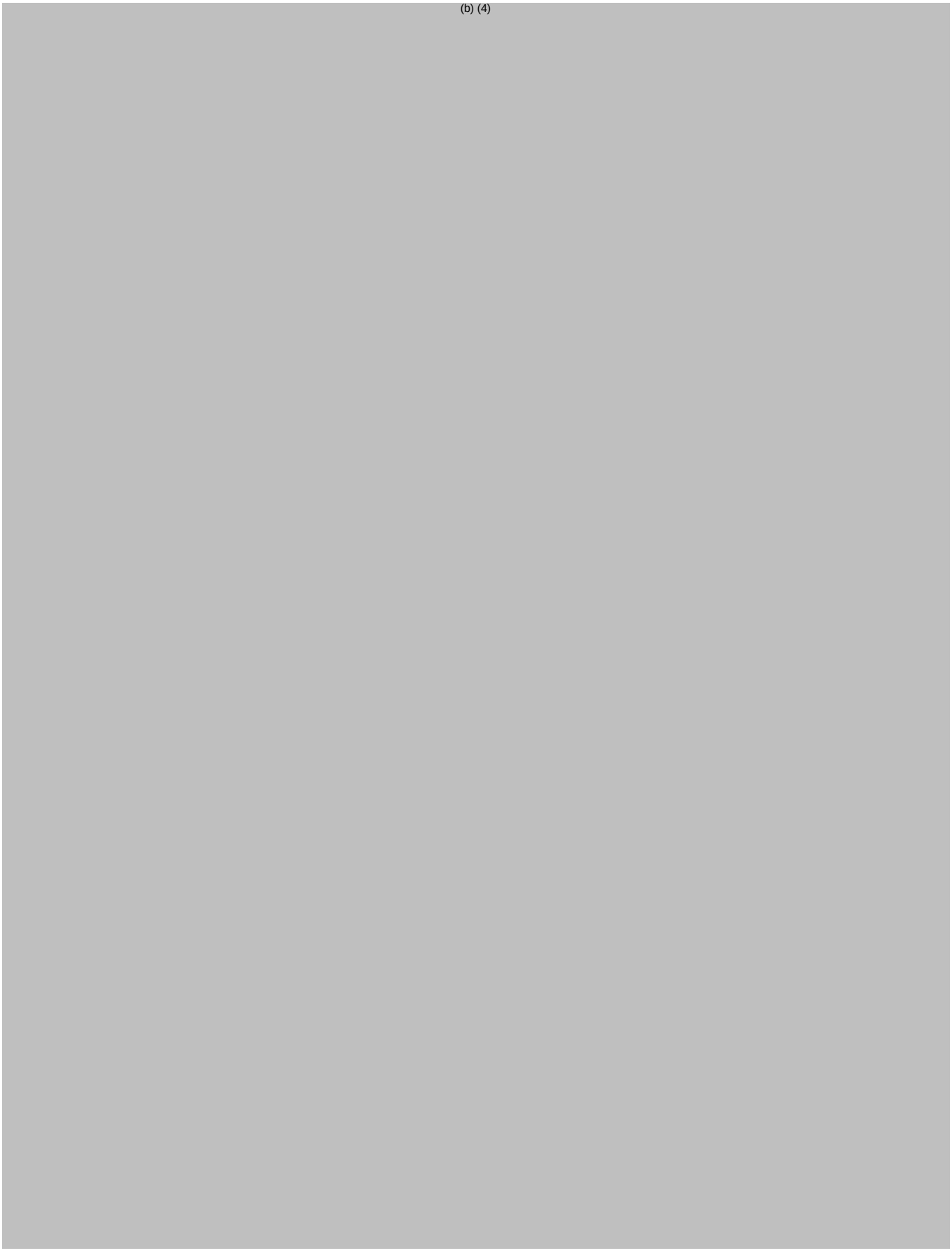

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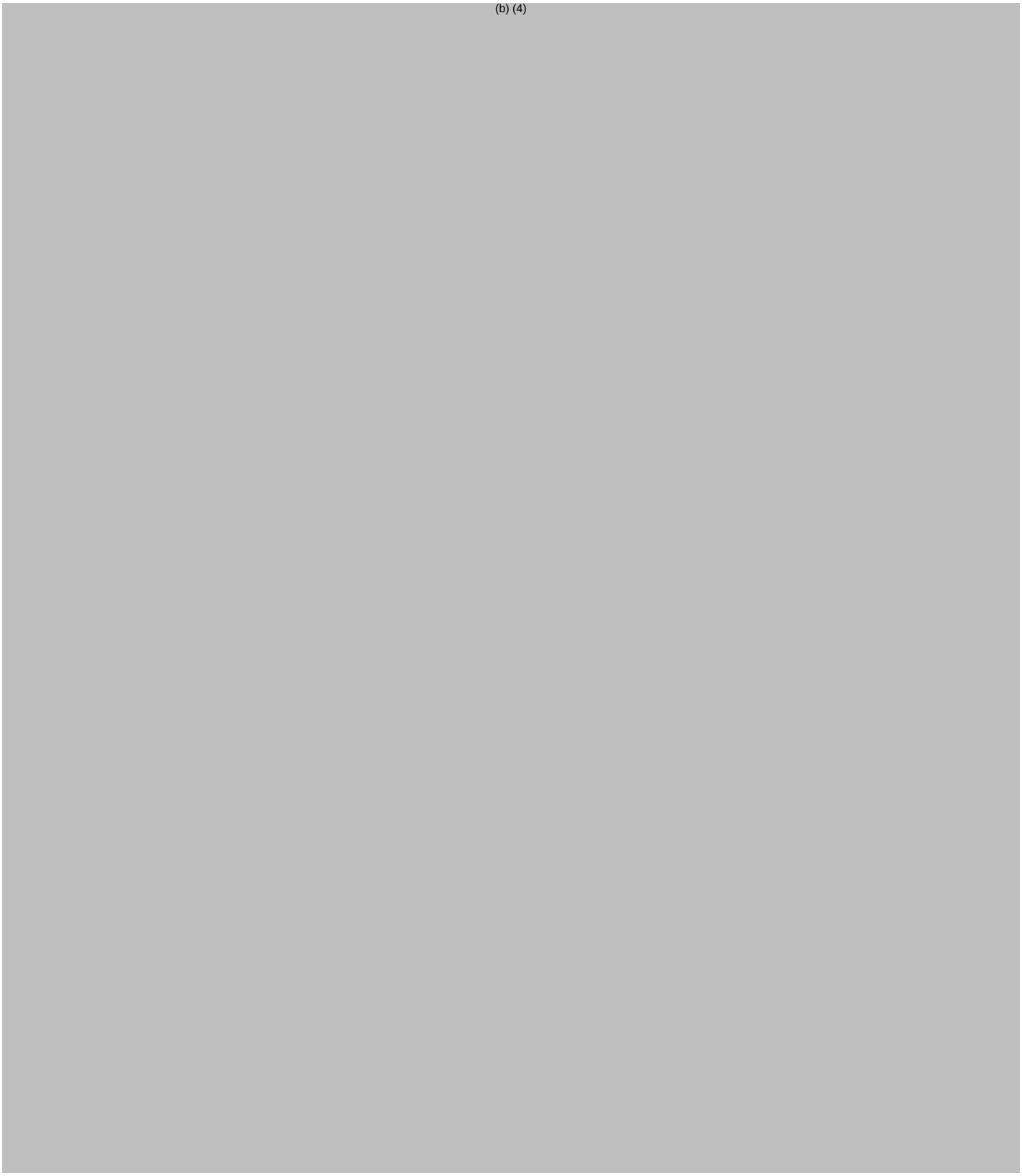

5.3 CONCLUSION

(b) (4)

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6 APPENDIX A: SURVEY QUESTIONS USED IN QUALITATIVE RESEARCH

The following survey questions were studied during the qualitative research interviews. A hard copy was sent to each participant as appropriate by stakeholder and returned to the research facility after the interviews were completed. Readers should note that survey content displayed in blue font represents alternative survey questions/responses developed for this research.

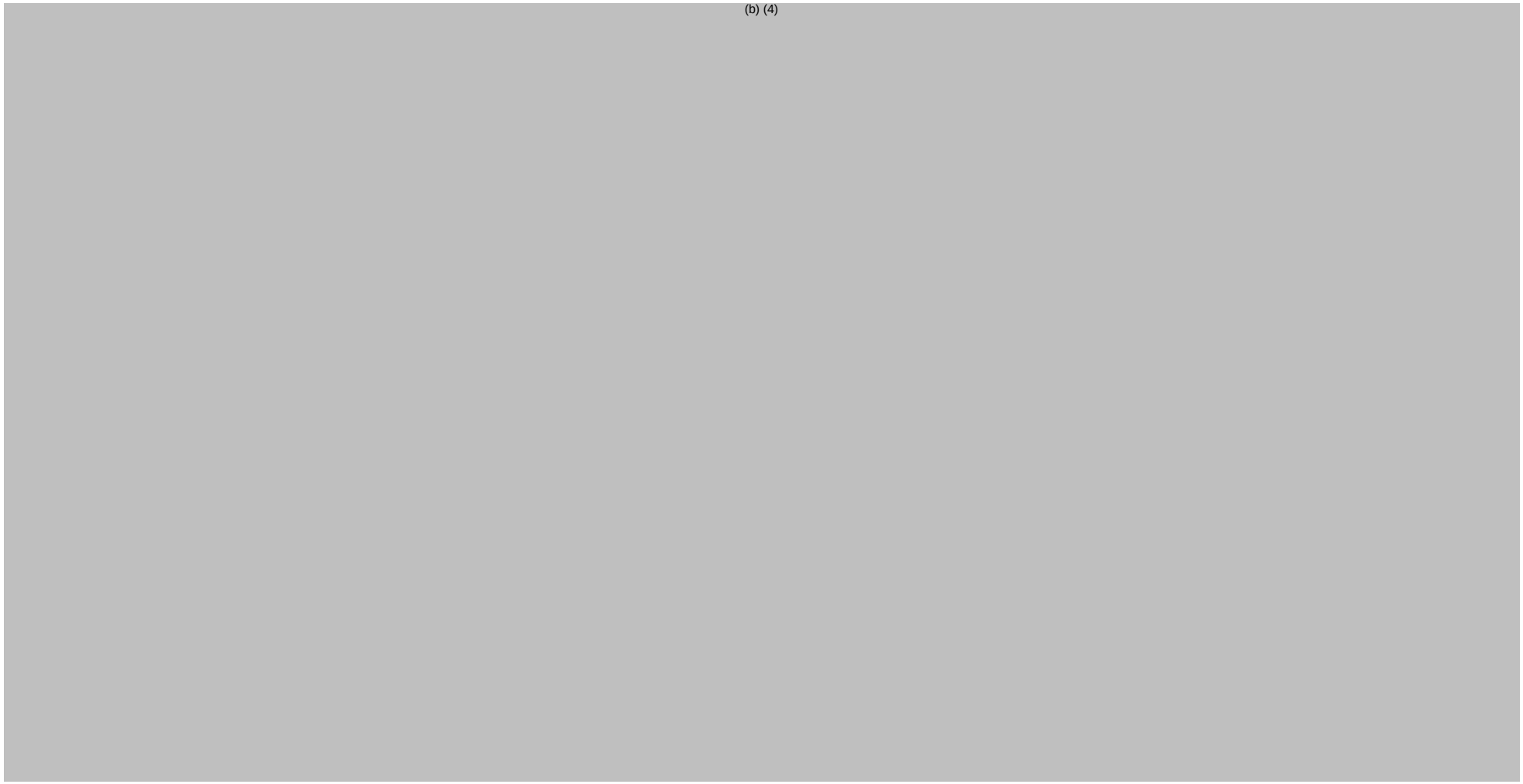
FDA_1597

TIRF Medicines Prescriber Survey

The Moderator will review the enclosed questions with you during the interview.

Please do not fill in the answer choices.

This document is only meant to guide your discussion with the Moderator.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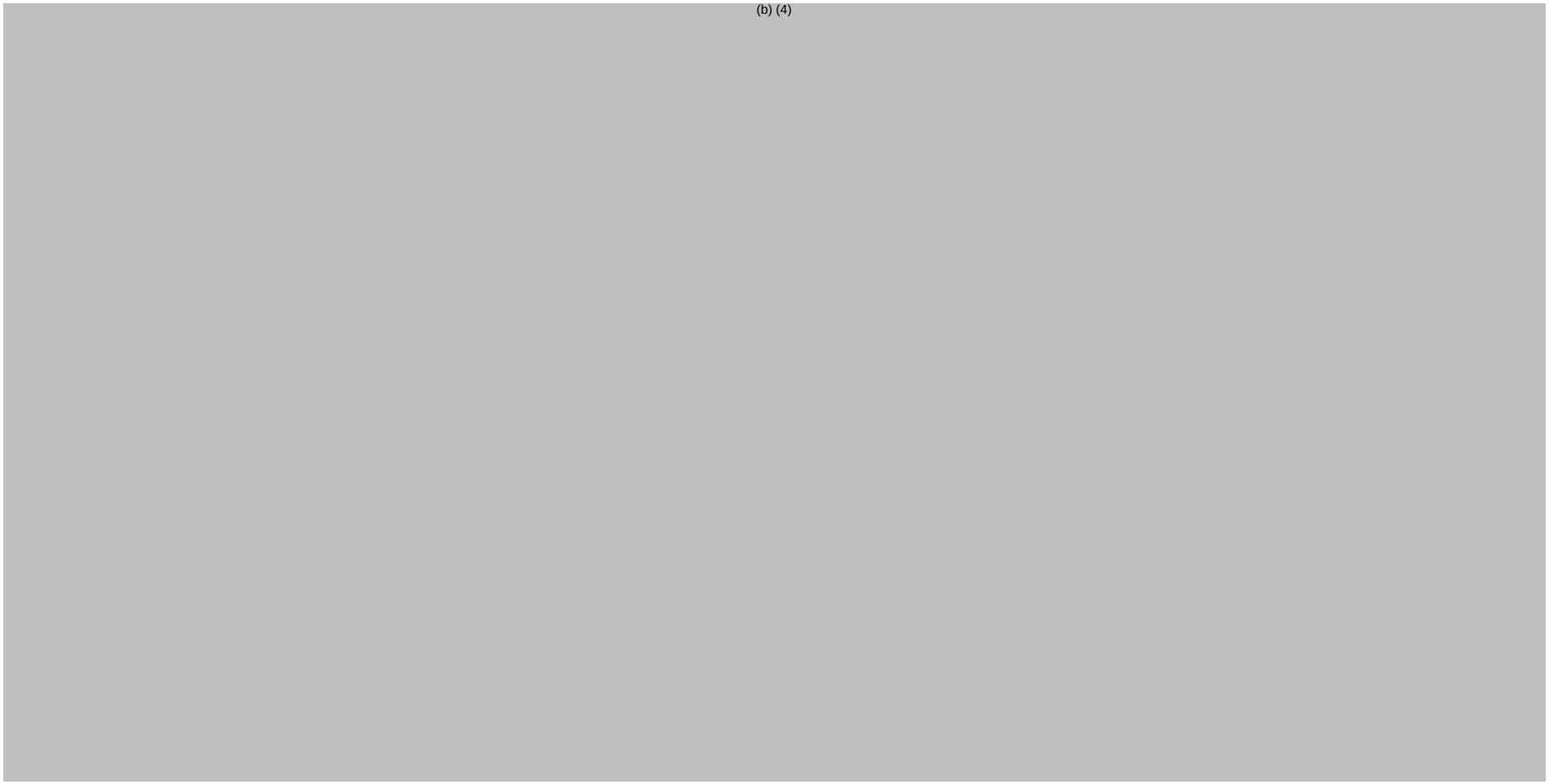
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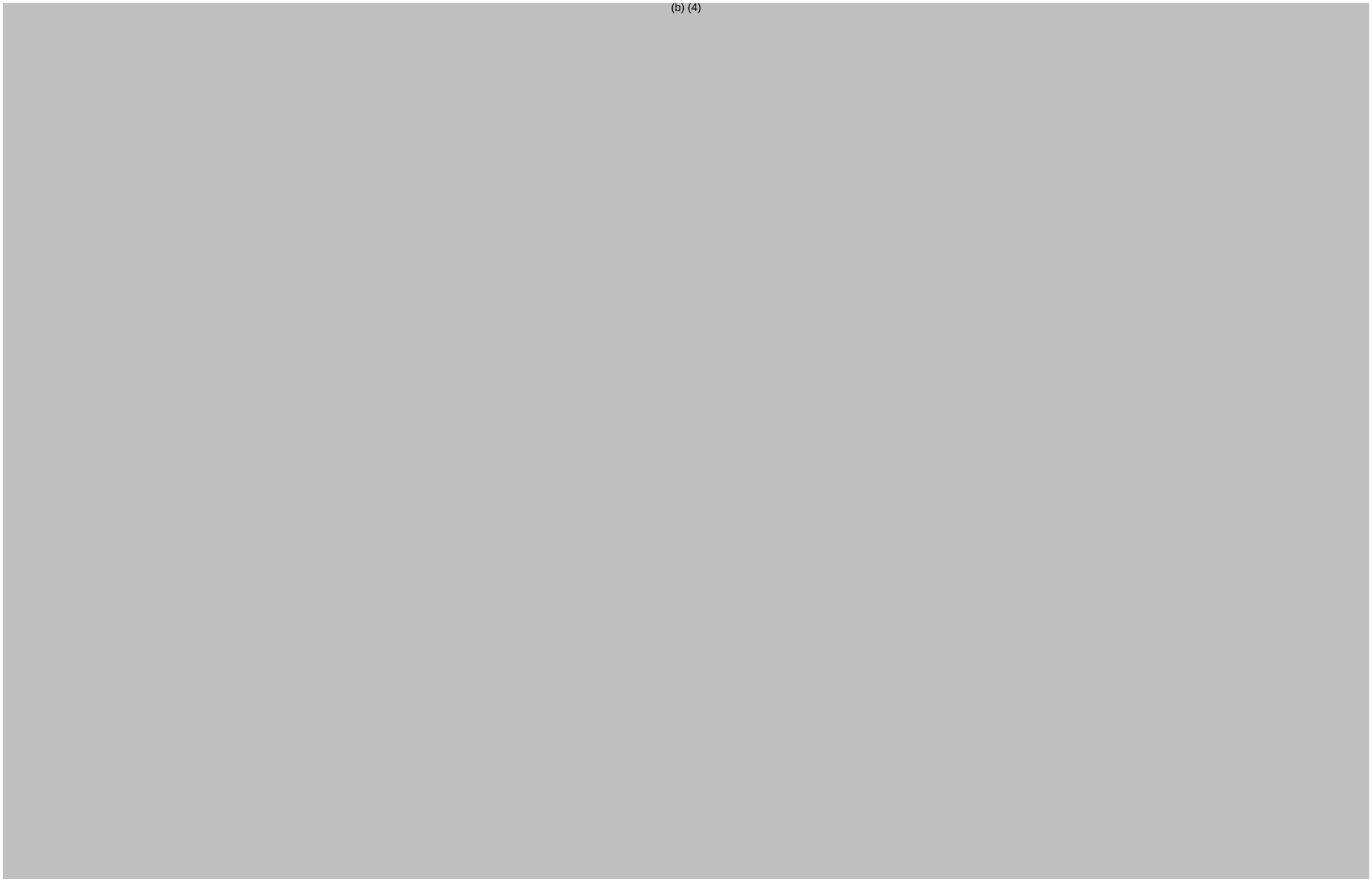

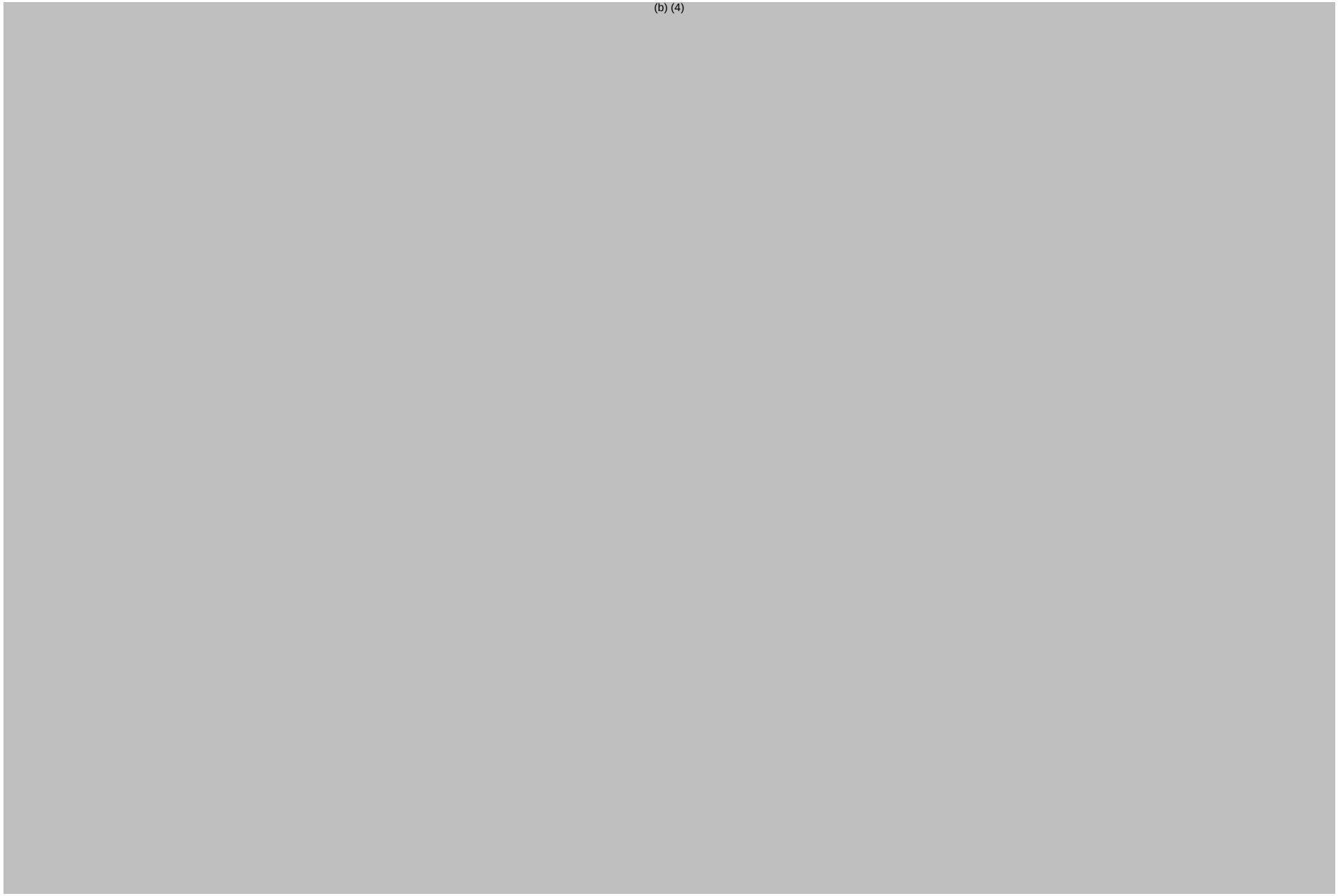
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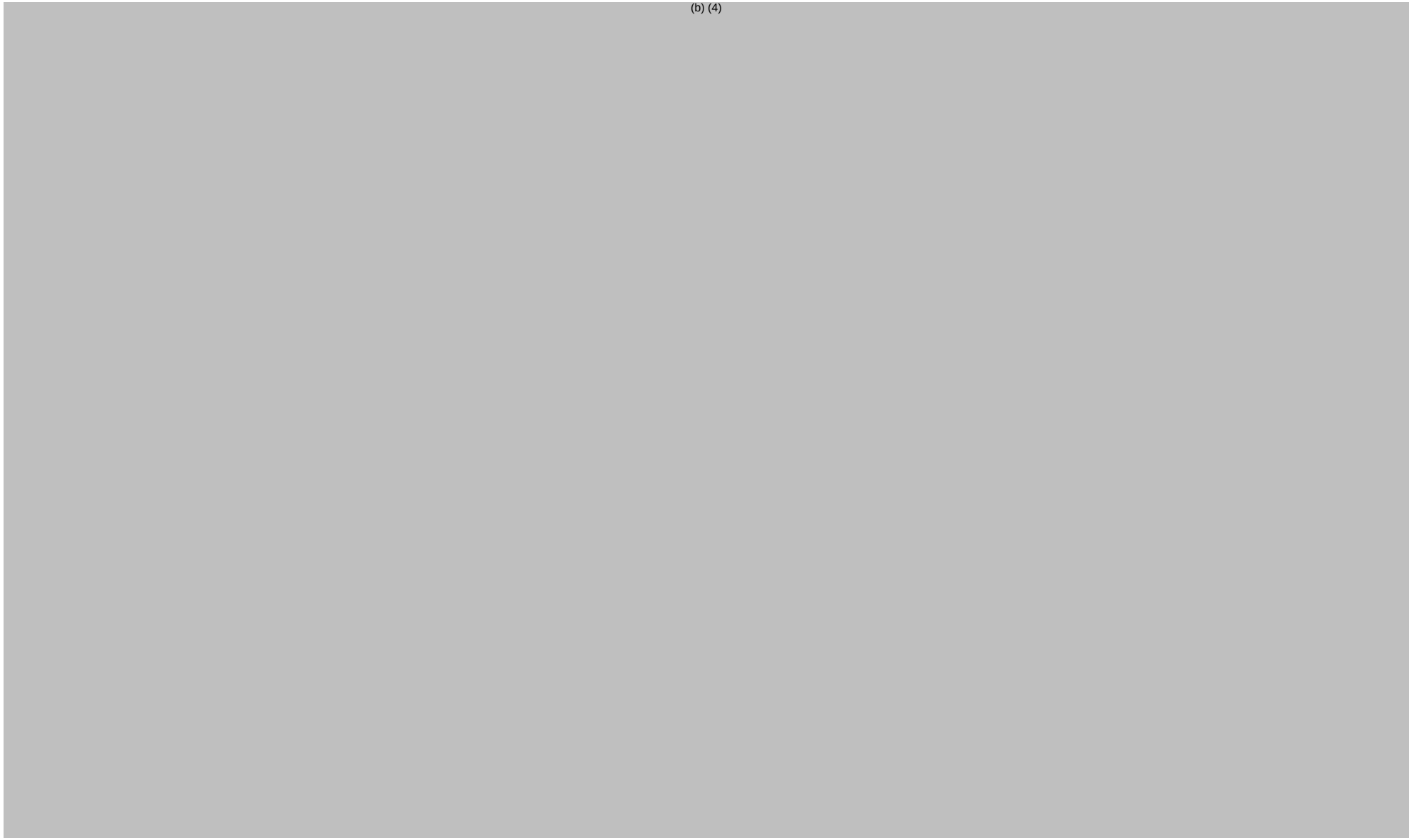


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TIRF Medicines Pharmacist Survey

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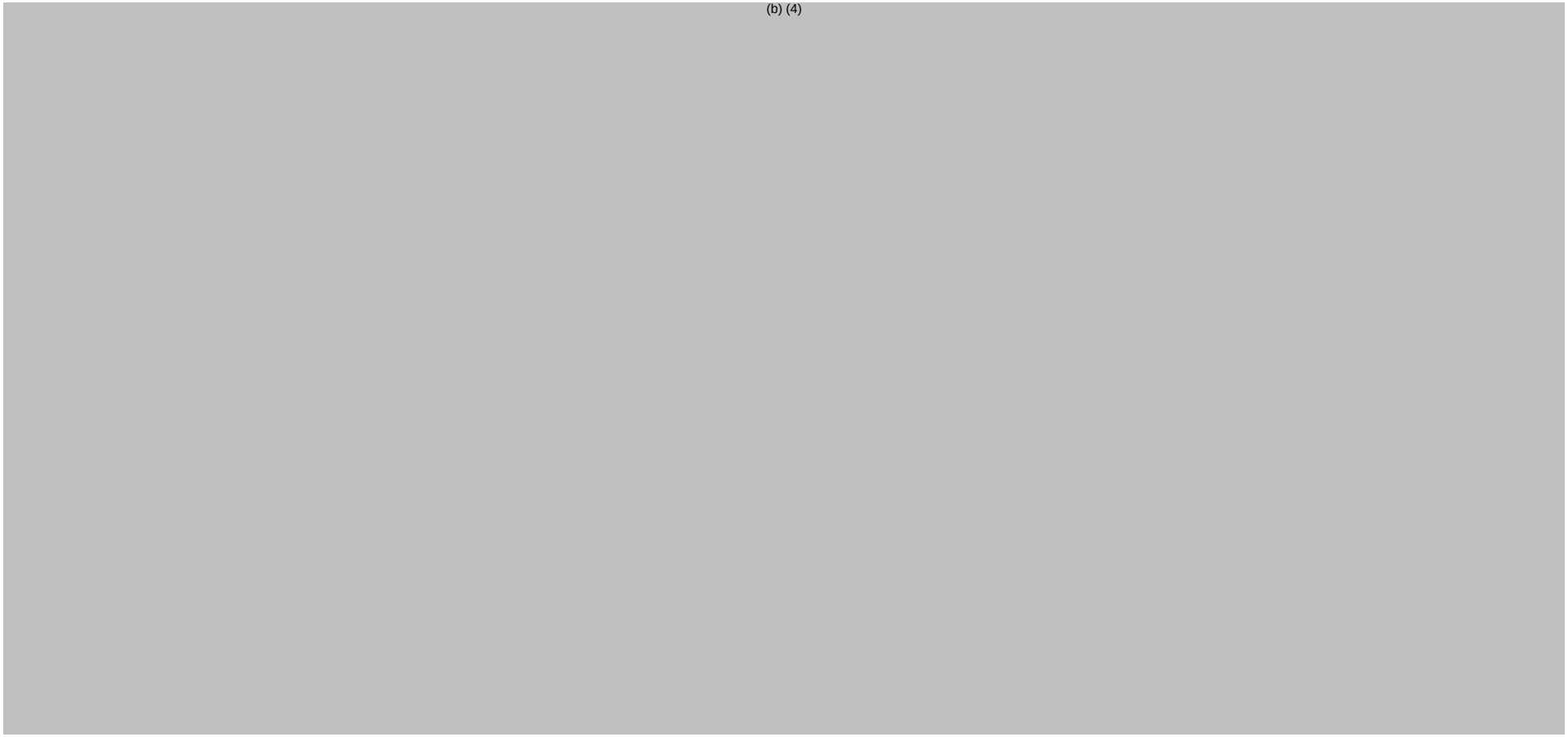
Please do not fill in the answer choices.

This document is only meant to guide your discussion with the Moderator.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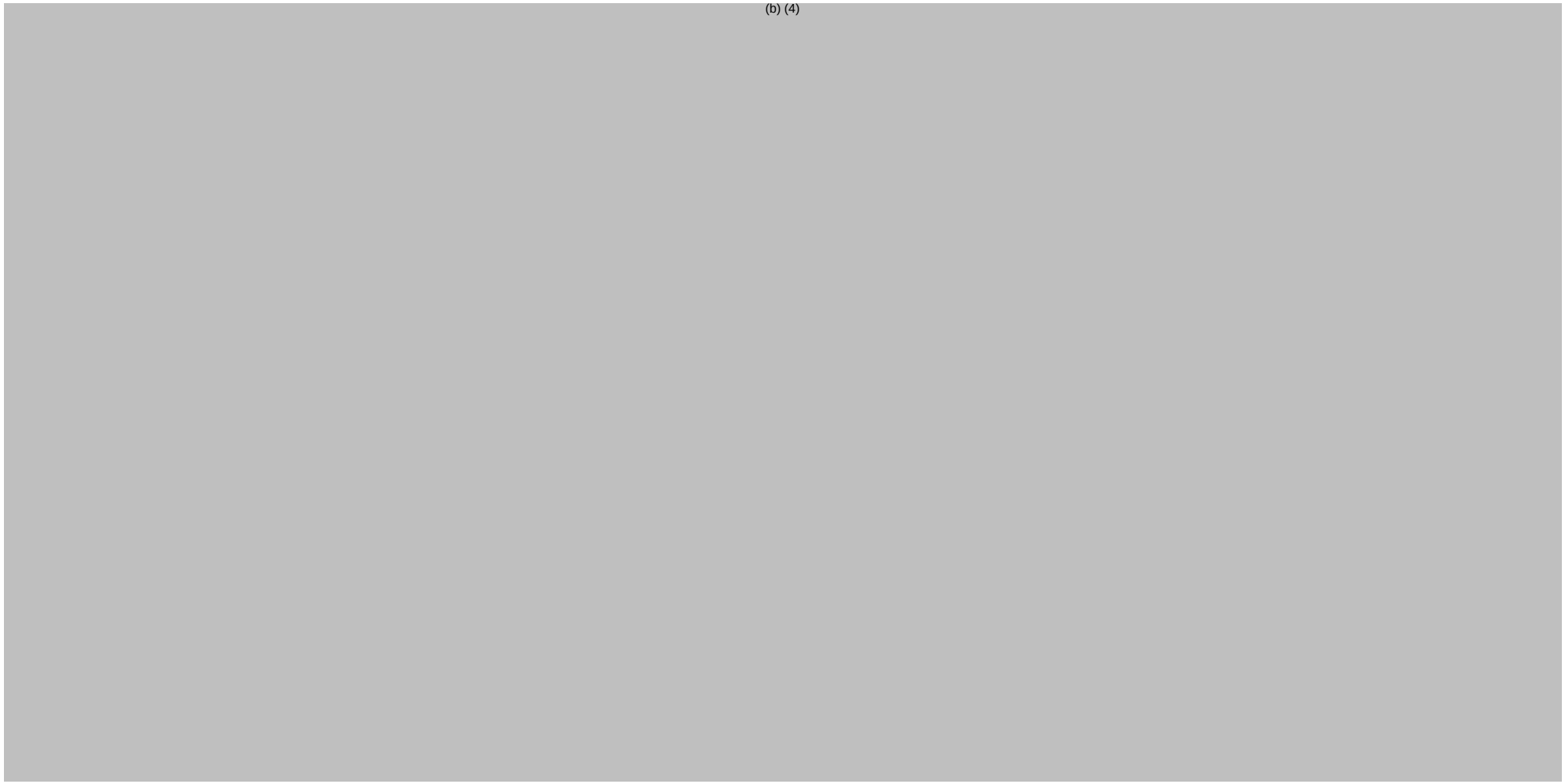
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Appendix D Prescriber Survey Protocol Track Change Document: Comparison of 12-month Survey to 24-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Archimedes Pharma US Inc.** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** ~~**Endo Pharmaceuticals Inc.**~~ **Galena Biopharma** **Insys Therapeutics** **Mallinckrodt**~~**, the Pharmaceuticals Business of Covidien**~~ **Meda Pharmaceuticals** **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**5**~~**4**~~**.0**
DATE:	**10 SEP**~~**23 May**~~ **2013**
APPROVED:	**FINAL**

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LIST OF APPENDICES

FDA_1612

1. LIST OF ABBREVIATIONS

CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE/PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

FDA_1613

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt, the Pharmaceuticals Business of Covidien; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a timetable for submission of assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI) of each product. This protocol will describe the administration of the surveys that will be conducted among prescribers who are enrolled in the TIRF REMS Access Program. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers who are enrolled in the TIRF REMS Access Program. Respondents who participate in the first wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the KAB survey results for prescribers included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions.

Qualitative research was performed with 7 prescribers who were recruited from the list of prescribers who completed surveys for the 12-month TIRF REMS Assessment and met the definition of "low performer," i.e., provided an incorrect response on 3 to 7 of the 10 targeted responses/questions from the 12-month TIRF REMS Assessment.

Among the prescribers interviewed, the need to provide a "frame-of-reference" for responding was frequent feedback. In addition, some of the findings suggest potential knowledge gap with respect to:

- Definition of opioid tolerance;
- How to convert patients from one TIRF medicine to another TIRF medicine; and
- Content pertaining to CYP3A4 inhibitors.

The findings from this research have been incorporated into the survey in Appendix A. The qualitative research report can be found in Appendix C.

4.1.2 Questions on REMS Goals

The Knowledge, Attitudes and Behaviors (KAB) questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- One question allowing for the respondent to list questions about the products or comments.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select "True," "False," or "I don't know" for each of the following.According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	**FALSE**

7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**
13	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	**13b.** Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

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Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
14	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	**14b.** The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines

		have different absorption properties and this could result in a fentanyl overdose.

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following question about behaviors will be asked after the key risk message questions:

Question 12: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of prescribers who are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. The text of the sample written invitation to prescribers can be found in Appendix B. If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-respondents from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of prescribers will be randomly selected.

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All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium to thank them for their participation. Prescribers who practice in Vermont, Massachusetts, or Minnesota and complete the survey will not receive compensation. Participants will be informed that prescribers from these states are not eligible to participate, but they and physicians who practice in these states will not receive compensation for their participation. The mailing will also include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of prescribers who are invited to participate will be a random sample of all enrolled prescribers. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

Prescribers will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 healthcare providers who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

All prescribers who are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Prescribers who have previously participated in the TIRF REMS KAB survey
- Prescribers or their immediate family members who have ever worked for ever worked for Anesta LLC, Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~; Meda Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; ProStrakan Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Prescriber-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of prescribers who do not have Internet access. It will also be convenient for prescribers to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the prescriber selects to participate in the survey online, he/she will be directed to a secured website to complete screening questions. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any time.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer interviews.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

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7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Gender
  - Medical degree of respondent: MD, DO, NP, PA
  - Medical specialty
  - Years of professional experience
  - How many times per month TIRF medicines prescribed in the last 6 months
  - Geographic region of practice

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible prescribers who completed all questions presented to them in the survey ("completers").

~~7.1.1~~7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

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~~7.1.2~~7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. ~~-~~ The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if there are questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE/PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE/PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 honorarium, a Thank You Letter, the correct responses to key risk messages, and the ISI after the survey is completed. Respondent contact information is also requested when necessary to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions in addition to instances where a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe TIRF medicines.

Appendix A Prescriber Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.
- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).
- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.
- **[BEGIN ONLINE/PHONE SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.
- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.
- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.
- **[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.
- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

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Survey Legend

- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

– New England Division - ME, NH, VT, MA, RI, CT
– Middle Atlantic Division - NY, NJ, PA

Midwest Region

– East North Central Division - OH, IN, IL, MI, WI
– West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

– South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
– East South Central Division - KY, TN, AL, MS
– West South Central Division - AR, LA, OK, TX

Survey Legend

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN ~~ONLINE/PHONE~~ SURVEY CONTENT]

[ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt; Meda Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal

Comment [24mos1]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

Comment [24mos2]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

~~T~~We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

Comment [24mos3]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Comment [24mos4]: FDA: please note that this underlined statement is presented online as a title heading of the following text to improve readability of the preamble Bolded text is not a hyperlink

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~: (a Pharmaceuticals Business of Covidien);~~ Meda Pharmaceuticals; Mylan, Inc; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

~~**[ONLINE ONLY]**How We Use Your Information~~

~~**[PHONE ONLY]**~~ Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

~~**[ONLINE ONLY]** How We Protect Your Privacy~~

[PHONE ONLY] Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

~~We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.~~

~~**[ONLINE ONLY]** How to Learn More about This Survey~~

~~**[ONLINE ONLY]** If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.~~

[PHONE ONLY] Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

~~**[ONLINE ONLY]** Taking the Survey~~

~~**[ONLINE ONLY]** Once you have answered a question and moved on, you cannot go back and change your answers.~~

~~**[ONLINE ONLY]** Thank you for your participation in this survey.~~

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[ONLY TERMINATE AFTER WAVE 1]**
   - ○ No
   - ○ I don't know **[ONLY TERMINATE AFTER WAVE 1]**

3. Are you enrolled in the TIRF REMS Access program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Anesta LLC **[TERMINATE]**
   - □ Archimedes Pharma US Inc. **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Endo Pharmaceuticals Inc. **[TERMINATE]**
   - □ Galena Biopharma **[TERMINATE]**
   - □ Insys Therapeutics **[TERMINATE]**

- ☐ Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~ **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Meda Pharmaceuticals **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ ProStrakan, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select "True," "False," or "I don't know" for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

[RANDOMIZE LIST]	True	False	I don't know
5a. Who are taking around-the-clock opioid therapy for underlying persistent chronic pain for one week or longer	○	○	○
5b. Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c. Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. A cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
7a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
7d.	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer "Yes," "No," or "I don't know" for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer "Yes," "No," or "I don't know" for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○

9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer "True," "False," or "I don't know" for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
10a. TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b. TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c. The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d. Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select "True," "False," or "I don't know" for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
11a. 8 mg oral hydromorphone/day	○	○	○
11b. 60 mg oral morphine/day	○	○	○
11c. 30 mg oral oxycodone/day	○	○	○
11d. 25 mcg transdermal fentanyl/hour	○	○	○
11e. 25 mg oral oxymorphone/day	○	○	○
11f. An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when prescribing TIRF medicines? Please answer "Always," "Only with the first prescription," "Sometimes," "Never," or "I don't know."

[RANDOMIZE LIST]	**Always**	**Only with the first prescription**	**Sometimes**	**Never**	**I don't know**

12a. Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b. Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c. Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d. Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e. Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f. Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.

[RANDOMIZE LIST]

13a. ○ Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.

13b. ○ Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

13c. ○ Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.

13d. ○ Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

13e. ○ I don't know

14. A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a

bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.

[RANDOMIZE LIST]

14a. ○ The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.

14b. ○ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

14c. ○ Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.

14d. ○ The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

14e. ○ I don't know

15. A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.

[RANDOMIZE LIST]

15a. ○ An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.

15b. ○ The dose that the prescriber believes is appropriate based on their clinical experience.

15c. ○ The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.

15d. ○ The median available dose.

15e. ○ I don't know

16. A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

16a. ○ Take another (identical) dose of the TIRF medicine immediately.

16b. ○ Take a dose of an alternative rescue medicine.

16c. ○ Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

16d. ○ Double the dose and take immediately.

16e. ○ I don't know

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17. A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.

[RANDOMIZE LIST]

17a. ○ The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.

17b. ○ Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.

17c. ○ There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.

17d. ○ The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

17e. ○ I don't know

18. Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select "True," "False," or "I don't know" for each of the following counseling statements.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
18a. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	○	○	○
18b. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	○	○	○
18c. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.	○	○	○
18d. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

19. Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?

- ○ Yes
- ○ No
- ○ I don't know

[PREAMBLE 2]

The next set of questions is about the educational materials for TIRF medicines and the TIRF Patient-Prescriber Agreement. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and generic versions of any of these brands.

20. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No **[GO TO Q24]**
- ○ I don't know **[GO TO Q24]**

23. Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

24. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]~~Q26]~~**
- ○ I don't know **[GO TO Q26~~Q~~26~~026~~]**

25. What are your questions? **[MULTILINE INPUT]**

26. Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?

- ○ Yes
- ○ No **[GO TO Q28]**
- ○ I don't know **[GO TO Q28]**

27. Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?

- ○ Yes
- ○ No
- ○ I don't know

28. Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?

- ○ Yes
- ○ No
- ○ I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

29. On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?

- ○ None **[GO TO DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

30. Please select the TIRF medicines that you have prescribed within the last 6 months (select all that apply):

- □ Abstral®
- □ Actiq® or generic Actiq®
- □ Fentora® ~~or generic Fentora®~~
- □ Lazanda®
- □ Onsolis®
- □ Subsys®

[DEMOGRAPHICS PREAMBLE 2] These last few questions are for demographic purposes.

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31. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

32. What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner ~~[Go to Q34]~~
- ○ Physician Assistant ~~[Go to Q34]~~
- ○ Prefer not to answer

33. In total, how many years have you been practicing medicine, since completing your education?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

34. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

35. What is your medical specialty?

- ○ Oncology
- ○ Primary care
- ○ Pain management
- ○ Other (please specify): _____
- ○ No designated specialty

[PHONE ONLY: BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[CLOSING 1]

We would like to send you a $125 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey. As a reminder, physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- ○ Yes
- ○ No **[SKIP TO CLOSING 2]**

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

36. Do you want to provide your telephone number?

○ Yes

○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[END CLOSING 2]

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

Appendix B Prescriber Invitation Letter

[CURR_DATE]

[PRESCRIBER NAME]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [PRESCRIBER NAME]:

You were selected to receive this letter because you have enrolled in the TIRF REMS Access Program. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys™, and generic versions of any of these brands.

The manufacturers of TIRF medicines (collectively referred to as the "TIRF REMS Industry Group") include Archimedes Pharma US Inc.; Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Endo Pharmaceuticals Inc.; Galena Biopharma; Insys Therapeutics; Mallinckrodt~~, the Pharmaceuticals Business of Covidien~~; Meda Pharmaceuticals; Mylan, Inc., and Par Pharmaceutical, Inc. These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and if required to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Prescribers who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating, go to **www.XXXXXXXXXX.com** anytime or call **1-877-379-3297,** 8AM to 8PM Eastern Time Monday through Friday. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.

Please have this letter with you at the time you take the survey. Thank you in advance for your help with this important effort.

Sincerely,

TIRF REMS Industry Group

* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Appendix C Qualitative Research Report

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