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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of the sixth (60 month, October 29, 2015 to October 28, 2016) Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for Transmucosal Immediate Release Fentanyl (TIRF) Agents

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TIRF Products

Drug Name	Dosage and Route	NDA/ ANDA	Applicant
Abstral	Sublingual Tablet	NDA 022510	Sentynl Therapeutics, Inc
Actiq	Oral Transmucosal Lozenge	NDA 020747	Cephalon, Inc.
Fentora	Buccal Tablet	NDA 021947	Cephalon, Inc.
Lazanda	Nasal Spray	NDA 022569	DepoMed, Inc.
Onsolis	Buccal Soluble Film	NDA 022266	BioDelivery Sciences International, Inc
Subsys	Sublingual Spray	NDA 202788	Insys Therapeutics, Inc
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 78907	Mallinckrodt, Inc
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 077312	Par Pharmaceutical, Inc
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 079075	Watson Laboratories, Inc.

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1. EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the 60-month risk evaluation and mitigation strategy (REMS) Assessment Report for the transmucosal immediate release fentanyl products (TIRF) shared system REMS, to determine if the goals of the REMS are being met. The TIRF REMS Access Program was approved in December 2011 to ensure the benefit of TIRFs outweighed the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. All the TIRF Sponsors have formed a consortium known as the TIRF REMS Industry Group (TRIG). The assessment report was submitted on December 28, 2016.

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

The 60-month assessment for the TIRF REMS includes data on certification/enrollment, distribution/dispensing, programmatic/infrastructure functioning and compliance, surveillance data (in the form of adverse event reports to the Sponsor and the Researched Abuse, Diversion, and Addiction Related Surveillance (RADARS)), a persistency analysis Phase II protocol assessing switches between TIRF products, as well as Patient, Prescriber, and Pharmacist knowledge and behavior (KAB) surveys.

The REMS assessment report is complete, however it is not meeting its stated goal nor most of the objectives. Key observations of the 60-month REMS assessment report include:

- The submitted surveillance data (spontaneously reported adverse events as well as RADARS data) contain a small number of events associated with TIRF products, especially in the RADARS Poison Center data, resulting in great variability in the data. However, **the data appear to indicate that for most outcomes assessed, TIRF event rates have increased over time.** In contrast, event rates for the composite comparators in most cases either decreased over time or had much smaller increases than those noted for TIRF products. A number of recommendations are provided for the TRIG such as the submittal of product-specific reports to facilitate our evaluation of any individual TIRF products that are driving the increases in adverse events over time.
- In the Supplemental Report, the TRIG used the IMS Health Longitudinal Prescription Database (LRx) to capture opioid dispensations prior to a TIRF

product dispensation to estimate **opioid tolerance**. Findings from individual NDA/ANDA submissions of opioid tolerance data generated via claims data indicate that regardless of the type of analysis, the proportion of opioid-non-tolerant patients receiving a TIRF product ranged from (b) (4) %. Because the proportion of patients receiving TIRFs as calculated by these analyses remains concerning, the **first objective** (prescribing only to appropriate/opioid-tolerant patients) is not being achieved. The TRIG is investigating the use of an alternative algorithm for the determination of opioid tolerance, and we have asked them to move forward with validating opioid tolerance algorithms, without delay. The validation studies may identify evidence of opioid tolerance that is not apparent in claims data, or they will confirm the poor adherence by prescribers to opioid-tolerance requirements.

- The TRIG's pharmacy switch database was the data source for the persistency analysis and uses outpatient TIRF prescription data. The persistency analysis examining TIRF product switches that were submitted in the 48-month REMS Assessment Addendum are difficult to interpret due to numerous methodologic concerns and thus resulted in the conclusion that it is not possible to tell if the **second objective** (prevention of inappropriate TIRF product interchanges) is being met. The TRIG is asked to re-submit these data using non-overlapping definitions and with numerators and denominators clarified.
- The data provided by the TRIG regarding the **third objective** (prevention of accidental exposure) are sparse and have many missing data elements. Therefore, it is not possible to determine whether this objective is being met. In multiple communications between FDA and the TRIG after the 60-month REMS Assessment Report, we have provided suggestions including the use of additional data sources for identification of unintentional pediatric exposures such as (e.g.) death certificate data as well as emergency department administrative claims data.
- Regarding the **fourth objective**, overall, patients, prescribers, and pharmacists had an adequate understanding of most of the key risk messages related to accidental exposure and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however all groups were less aware of the need to only prescribe and dispense TIRF medicines to appropriate patients (opioid-tolerant) than they were of other components of the TIRF REMS program. Although the respondents had adequate understanding of most of the key risk messages, the surveys were not based on probability random samples and had high non-response rate. Some results indicate that those who volunteered to respond to the surveys had different characteristics than those who were targeted to answer the surveys (e.g. education level). Therefore, the survey results may be biased and may not be generalizable to the general population of patients who received a TIRF prescription, TIRF prescribers, and pharmacists who dispensed a TIRF prescription. Given the

survey results, we conclude that this objective is being partially met, and request the TRIG continue to provide comparisons of the baseline characteristics between survey respondents and general population

- Concerns with the REMS's compliance program are noted to the TRIG, such as: the number of patients enrolled by the prescriber without a complete PPAF on file needed to be considered a non-compliance event; the TRIG's corrective action processes; and the passive nature of detecting non-compliance events
- Concerns with some of the TRIG's administrative processes are noted to the TRIG such as the increasing median prescription processing time after at least one initial REMS-related rejection; lack of sufficient REMS process reminders in the closed governmental systems; the fact that the reason prescribers/pharmacies choose to leave the REMS is unknown; low numbers of inpatient pharmacies audited.

We have determined that the TIRF REMS is not meeting its overall goal or most of the objectives.

2. INTRODUCTION

This review evaluates the 60-month REMS assessment report for the transmucosal immediate-release fentanyl (TIRF) products risk evaluation and mitigation strategy (REMS) to determine if the report is complete and if the goals of the TIRF REMS Access Program REMS are being met. The assessment period covers October 29, 2015 to October 28, 2016. This is the 6th REMS assessment for the TIRF REMS. The report was submitted to the TIRF drug master file (DMF) on December 28, 2016, with a Supplemental report submitted February 17, 2017. Data regarding opioid tolerance were submitted to 7 NDA/ANDAs on June 15, 2017, and additional data/responses were submitted by the TRIG on October 16, 2017 in response to an October 2, 2017 telecon between the FDA and the TRIG.

3. BACKGROUND

TIRFs are short-acting high-potency opioid analgesics indicated in the management of breakthrough pain in cancer patients. A primary safety concern with all the TIRFs is their use in opioid non-tolerant patients due to the potential of life-threatening respiratory depression in patients not already taking and tolerant to chronic opioid analgesics. In addition, cases of diversion, abuse, overdose, misuse, and prescribing to opioid-non-tolerant patients have led to serious adverse events or fatalities, further demonstrating that these products can pose a serious and significant public health concern. Thus, FDA determined that a REMS was necessary to ensure the benefits outweigh the risks of misuse, abuse, addiction,

overdose, and serious complications associated with the use of TIRF medicines. However, in 2010, the FDA also determined that, in the interest of public health and to minimize the burden on the healthcare system, *a single*, *shared* REMS should be implemented for all members of the TIRF class and on December 28, 2011, the "TIRF REMS" was approved for Abstral, Actiq, Fentora, Lazanda, Onsolis, and generic versions of these TIRF medicines. On January 4, 2012, the FDA approved Subsys, as well as its inclusion into the TIRF REMS Access program. The TIRF REMS Access program was launched on March 12, 2012, approximately 11 weeks after REMS approval. Implementation of the TIRF REMS for closed system pharmacies[1] was launched on June 30, 2012.

The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Insys Therapeutics Inc., Mallinckrodt Pharmaceuticals, Mylan, Inc. , Par Pharmaceutical, Inc., and Sentynl Therapeutics, Inc.). The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. The 60-month assessment report was prepared by United BioSource Corporation (UBC).

The **goals** of the TIRF REMS Access program 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.

3.1. REMS ELEMENTS

The TIRF **REMS elements** include:

- A **Medication Guide -** a product-specific TIRF Medication Guide will be dispensed with each TIRF prescription. These Medication Guides are available on the TIRF REMS Access website (www.TIRFREMSaccess.com).
- **Elements to Assure Safe Use (ETASU)** – details include:
  - (ETASU A) training and certifying outpatient TIRF prescribers;
  - (ETASU B) training and certifying pharmacies who dispense TIRFs;

[1] Closed systems are defined as "integrated healthcare systems that dispense for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required."

- (ETASU C) assurances that TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions;
    i. patients are enrolled when their first prescription is processed at a pharmacy;
    ii. a completed Patient-Prescriber Agreement Form (PPAF) must 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;
    iii. a maximum of three prescriptions are allowed within 10 working days from when the patient had their first prescription filled with no additional dispensations allowed until a completed PPAF is received;
    iv. upon receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the pharmacist enters the prescription details in their pharmacy management system (PMS) and sends the transaction to the TIRF REMS Access program via a switch provider to ensure that all elements meet the requirements of the TIRF REMS Access program;

- An **Implementation System** involves training and enrolling wholesalers/distributors who distribute TIRFs. The TRIG is required to maintain databases of prescribers, pharmacies, patients, and distributors, as well as develop a TIRF Access System;
- The **Timetable** for submission of REMS Assessment Reports was at 6 and 12 months for the first year then annually thereafter to be submitted on or before December 28th of each year.

The TIRF REMS **Assessment Plan** can be found in **Appendix Section 10.1** of this review**.**

3.2. FINDINGS FROM PREVIOUS ASSESSMENT

The 48-month assessment report for the TIRF REMS was finalized on September 28, 2016. **On November 10, 2016, the TRIG was issued a REMS Assessment Acknowledgement Letter (RAAL)** stating that the REMS Assessment was complete but that it was not possible to determine whether the overarching goal of the REMS - to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors - was being met.

The first objective (prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients) was not being achieved since approximately 42% of patients prescribed TIRF products were not opioid tolerant. The TRIG was told to further investigate this concerning finding and that at a minimum, further evaluation of this finding needed to include product-

specific assessment of opioid tolerance that each member sponsor will submit only to their NDA or ANDA

It was not possible to determine if the second objective (preventing inappropriate conversion between TIRF medicines) was being met, although a persistency analysis provided by the TRIG indicated that the number of patients who may be exposed to inappropriate conversion between TIRF medicines may be as high as 17.1-20.5%.

It was also not possible to determine if the third objective (preventing accidental exposure to children and others for whom it was not prescribed) was being met since only a few case reports were presented and included little detail,

The fourth objective (educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines) was partially met. Overall, while patients, prescribers, and pharmacists seemed to have an adequate understanding of most of the key risk messages, all of these stakeholders had a lower awareness of the need to only prescribe and dispense TIRF medicines to appropriate (opioid-tolerant) patients. The RAAL can be found in **Appendix Section 10.2**.

3.3. REMS MODIFICATION

On April 10, 2017, the TRIG Sponsors were issued a REMS Modification Notification Letter as a result of approval of the safety labeling changes on December 16, 2016. The REMS modification that incorporated those changes was approved in September 2017. Those labeling changes strengthened the warnings regarding the risks of misuse, abuse, addiction, overdose, death and neonatal opioid withdrawal syndrome; serotonin syndrome with concomitant use of serotonergic drugs; adrenal insufficiency; androgen deficiency; and profound sedation, respiratory depression, coma, and death associated with the concomitant use of opioid analgesics and benzodiazepines or other central nervous system depressants, including alcohol.

4. REVIEW MATERIALS REVIEWED

- August 17, 2001 Actiq Periodic Safety Update Report (PSUR)-16, Supporting Document #102
- April 15, 2008 Fentora RiskMap 5th Quarterly Report, Supporting Document #94
- May 4, 2016 48-Month REMS Supplemental Assessment Report
- November 10, 2016 REMS Assessment Acknowledgement Letter from DAAAP (J. Racoosin)

- December 28, 2016, 60-month TRIG Assessment Report submitted by the TRIG
- February 17, 2017, TRIG supplemental submission to the 60-month REMS Assessment Report.
- March 10, 2017 TRIG response to the March 3, 2017 TRIG-FDA teleconference
- March 21 FDA email to the TRIG regarding opioid tolerance
- March 31, 2017 TRIG response to the March 3, 2017 TRIG-FDA teleconference
- April 10, 2017 REMS Modification Notification Letter from DAAAP (J. Racoosin)
- April 10, 2017 (accessed) "What are Transmucosal Immediate-Release Fentanyl (TIRF products?" TIRF REMS webpage http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60
- April 21, 2017 DEPI II (T. Meyer) Consult Review of NEISS-CADES Data on Pediatric Emergency Department Visits Related to Accidental Exposure to Transmucosal Immediate Release Fentanyl
- May 2, 2017 DEPI II (D.T. Coyle and T. Pham) Consult Review of 48-Month Transmucosal Immediate-Release Fentanyl (TIRF) Product REMS Assessment Data
- May 5, 2017 TRIG response to the April 28, 2017 FDA Information Request (IR)
- May 30, 2017 TRIG response to the April 28, 2017 FDA IR
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: NDA 22510;Name: Abstral
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: NDA 20747;Name: Actiq
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: ANDA 77312
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: ANDA 79075
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: NDA 21947;Name: Fentora
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: NDA 22569;Name: Lazanda
- June 15, 2017, TIRF REMS Access Program Assessment—Use of Individual Products: NDA 202788;Name: Subsys
- July 20, 2017 Pharmacovigilance Consult Review from DPV II (C. Patel) regarding TIRF accidental exposures and off label use
- August 4, 2017 DEPI II (T. Meyer) Consult Review of 60-Month Transmucosal Immediate-Release Fentanyl (TIRF) Product REMS Assessment Data

- August 24, 2017 response from TEVA to an August 10, 2017 FDA information request (IR) regarding older opioid tolerance data for Fentora
- August 31, 2017 response from TEVA to an August 17, 2017 FDA information request (IR) regarding older opioid tolerance data for Actiq
- August 31, 2017 Memo from DEPI (T. Meyer) providing responses to the TRIG's responses Dated March 31, 2017
- September 19, 2017 DB7 (R. Zhang) Statistical Review and Evaluation for TIRFs
- October 16, 2017 TRIG response to FDA questions from an October 2, 2017 telecon between the FDA and the TRIG
- November 2, 2017 TRIG response to an October 27, 2017 FDA IR
- November 15, 2017 Memo from DEPI (T. Meyer) providing responses to the TRIG's responses Dated October 16, 2017.

5. REVIEW OF 48-MONTH ASSESSMENT REPORT

5.1. ASSESSMENT ELEMENT 1: UTILIZATION

The first element of the Assessment Plan states:

> *1. The TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively):*
>
> *a. <u>Patient Enrollment:</u>*
>
> *a. Number of unique patients enrolled*
>
> *b. Number of patients inactivated*
>
> *b. <u>Prescriber Enrollment:</u>*
>
> *a. Number of prescribers enrolled*
>
> *b. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;*
>
> *c. Number of prescribers inactivated*
>
> *c. <u>Pharmacy Enrollment:</u>*
>
> *a. Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities);*
>
> *b. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);*
>
> *c. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);*
>
> *d. <u>Distributor enrollment:</u>*
>
> *a. Number of distributors enrolled;*

b. Number of distributors inactivated;

Patients:

During the current reporting period, there were **4,225 newly enrolled patients** (compared to 8,740 the previous reporting period), resulting in a cumulative total of 42,164 patients enrolled in the TIRF REMS. In a May 5, 2017 response from the TRIG to an April 28, 2017 Information Request (IR)[2] from the FDA, the TRIG verified the 4,225 newly enrolled patients total. In the assessment report the TRIG states that "…*by the design of the program, a patient enrollment status will never change to inactivated*." However, in the May 5, 2017 response, the TRIG states that *"Patients remain passively enrolled in the program from reporting period to reporting period as long as they continue therapy. Therefore, the number of newly enrolled patients may decrease from year to year as more patients may be continuing therapy and not initiating therapy."*

Prescribers:

At the end of this reporting period there were **8,151 prescribers currently enrolled** (9,096 were enrolled last year). This current total includes 1,446 newly enrolled prescribers, 2,631 prescribers who re-enrolled and 4,074 who remain active from a previous period. Cumulatively there have been 16,549 prescribers who have successfully completed enrollment in the program.

- Inactivations:

A total of 3,635 prescribers were inactivated at some point during the current reporting period, 99.5% (3,616) were due to expiration of enrollment (prescribers are required to re-enroll every 2 years in the REMS). Of those 3,616 prescribers whose enrollment expired at some point during the current reporting period, 2,763 (76.4%) remained expired at the end of the reporting period. In total, 8,401 prescribers remained inactivated at the end of the reporting period.

During the current reporting period;

- 54 prescribers attempted enrollment but enrollment was pending 3 to 6 months later;
- 194 prescribers had their enrollment pending for more than 6 months

- Pending Enrollments

The primary reasons for prescriber enrollments pending for 3-6 months were for "training not complete" (83%) and "no attestation" (82%). The primary reasons for

[2] The April 28, 2017 IR asked the TRIG to verify the number of newly enrolled patients is 4225. We note that this number is less than half of the 8740 newly enrolled patients reported in the December 2015 TIRF REMS Assessment report.

enrollments for more than 6 months were for similar reasons, “no attestation” (75%) and “training not complete” (62%).

Pharmacies:

The total number of pharmacies in the program (newly enrolled/re-enrolled or previously enrolled) are presented in **Table 1**, data taken from the TRIG’s Table 8:

Table 1: Pharmacy Enrollments

Parameter	Current Reporting Period		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Total Number of Pharmacies Enrolled as of the End of this Reporting Period	42,433	232	42,665
Chain Pharmacy Stores	37,535 (88.5%)	N/A	37,535 (88.0%)
Independent Outpatient Pharmacies	4,060 (9.6%)	N/A	4,060 (9.5%)
Inpatient Pharmacies	760 (1.8%)	N/A	760 (1.8%)
Chain Pharmacy Headquarters	78 (0.2%)	N/A	78 (0.2%)
Closed System Headquarters	N/A	6 (2.6%)	6 (<0.1%)
Closed System Pharmacies	N/A	226 (97.4%)	226 (0.5%)
Total Number of Newly Enrolled Pharmacies	1,529 (5.8%)	8 (3.5%)	1,537 (5.8%)
Chain Pharmacy Stores	1,026 (67.1%)	N/A	1,026 (66.8%)
Independent Outpatient Pharmacies	387 (25.3%)	N/A	387 (25.2%)
Inpatient Pharmacies	114 (7.5%)	N/A	114 (7.4%)
Chain Pharmacy Headquarters	2 (0.1%)	N/A	2 (0.1%)
Closed System Headquarters	N/A	0	0
Closed System Pharmacies	N/A	8 (100.0%)	8 (0.5%)
Total Number of Re-Enrolled Pharmacies	24,787 (94.2%)	219 (96.5%)	25,006 (94.2%)
Chain Pharmacy Stores	22,043 (88.9%)	N/A	22,043 (88.2%)
Independent Outpatient Pharmacies	2,260 (9.1%)	N/A	2,260 (9.0%)
Inpatient Pharmacies	439 (1.8%)	N/A	439 (1.8%)
Chain Pharmacy Headquarters	45 (0.2%)	N/A	45 (0.2%)
Closed System Headquarters	N/A	5 (2.3%)	5 (<0.1%)
Closed System Pharmacies	N/A	214 (97.7%)	214 (0.9%)
Number of Pharmacies that Remain Enrolled from the Previous Reporting Period	16,118	5	16,123
Chain Pharmacy Stores	14,466 (89.8%)	N/A	14,466 (89.7%)
Independent Outpatient Pharmacies	1,414 (8.8%)	N/A	1,414 (8.8%)
Inpatient Pharmacies	207 (1.3%)	N/A	207 (1.3%)
Chain Pharmacy Headquarters	31 (0.2%)	N/A	31 (0.2%)
Closed System Headquarters	N/A	1 (20.0%)	1 (<0.1%)
Closed System Pharmacies	N/A	4 (80.0%)	4 (<0.1%)

Percentages are based on the total number (N) of pharmacies with enrollment activity in this reporting period; The number of Chain Pharmacy Headquarters and Closed System Headquarters may not be associated with the number of Chain Pharmacy Stores and Closed System Pharmacies, respectively Chain Pharmacy Stores or Closed System Pharmacies may be associated with a Headquarter enrolled in a previous reporting period

As compared to 42,433 non-closed system pharmacies enrolled this reporting period, 42,968 were enrolled last reporting period. Chain pharmacies make up the vast majority (88.5%) of pharmacy types in the TIRF REMS program, while independent pharmacies comprise 9.6%. In the TRIG’s May 30, 2017 response to

the Agency's April 28, 2017 IR, the TRIG states that: "*The TIRF REMS Access program defines independent outpatient pharmacies as "retail, mail order, or institutional outpatient pharmacies*".

The vast majority of closed system pharmacies (214/232 = 92%) re-enrolled this reporting period.

Tables 2 and **3** (adapted from the TRIG's Table 9) summarizes pharmacy inactivations by pharmacy type and include the reasons for the inactivations during the current reporting period:

Table 2: **Pharmacy Inactivations by Pharmacy Type**

Parameter	Current Reporting Period		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Number of Pharmacies that Became Inactivated During this Reporting Period	4,530	206	4,736
Chain Pharmacy Stores	3,043 (67.2%)	N/A	3,043 (64.3%)
Independent Outpatient Pharmacies	1,222 (27.0%)	N/A	1,222 (25.8%)
Inpatient Pharmacies	252 (5.6%)	N/A	252 (5.3%)
Chain Pharmacy Headquarters	13 (0.3%)	N/A	13 (0.3%)
Closed System Pharmacies	N/A	206 (100%)	206 (4.3%)
Numbers of Pharmacies Inactivated in This Time Period that Remain Inactivated at End of Reporting Period	2,610	39	2,649
Chain Pharmacy Stores	1459 (55.9%)	N/A	1459 (55.1%)
Independent Outpatient Pharmacies	942 (36.1%)	N/A	942 (35.6%)
Inpatient Pharmacies	204 (7.8%)	N/A	204 (7.7%)
Chain Pharmacy Headquarters	5 (0.2%)	N/A	5 (0.2%)
Closed System Pharmacies	N/A	39 (100%)	N/A
Cumulative Number of Pharmacies Ever Inactivated	16,763	360	17,123

Table 3: Reasons for Inactivations by Pharmacy Type

Reasons for Inactivation by Pharmacy Type	
Reason(s) for Chain Pharmacy Store Inactivation	
Enrollment Expired	2,819 (92.6%)
Program Opt-Out	224 (7.4%)
-----Enrollment remained expired at end of period	1,242 (44.1%)
Reason(s) for Independent Outpatient Pharmacy Inactivation	
Enrollment Expired	1,214 (99.3%)
Program Opt-Out	8 (0.7%)
-----Enrollment remained expired at end of period	934 (76.9%)
Reason(s) for Inpatient Pharmacy Inactivation	
Enrollment Expired	249 (98.8%)
Program Opt-Out	3 (1.2%)
-----Enrollment remained expired at end of period	201 (80.7%)
Reason(s) For Closed System Pharmacy Inactivation	
Enrollment Expired	206 (100.0%)
-----Enrollment remained expired at end of period	39 (18.9%)
Reason(s) for Chain Pharmacy Headquarters Inactivation	
Enrollment Expired	12 (92.3%)
Program Opt-Out	1 (7.7%)
-----Enrollment remained expired at end of period	4 (33.3%)

Of the 4,530 pharmacies inactivated this reporting period, **57.6%** (2,610) remained inactivated at the end of the reporting period. The reasons for inactivation were 0.7 – 7.4% due to "program opt out" and 93-99% due to "enrollment expired." Interestingly, while 48% of the chain stores that became inactivated this reporting period remained inactivated at the end of the reporting period, 77% of independent stores that became inactivated this reporting period remained so at the close of the period.

Table 4 below (adapted from TRIG Assessment report, Table 10) presents the number and reasons for pending pharmacy enrollments for those enrollments pending for either 3-6 months or >6 months:

Table 4: Numbers of Pharmacies Pending Enrollments for ≥3 – 6 months and >6 months and Reasons for Pending Enrollments

Parameter	Current Reporting Period	
	Pharmacies Pending Enrollment ≥3 – 6 Months	Pharmacies Pending Enrollment >6 Months
Number of Pharmacies Who Attempted Enrollment but are Still Pending Enrollment	39	209
Reasons for Pending Enrollment		
Pending Test Transaction Verification	46%	54%
No Attestation	46%	40%
Training not complete	31%	35%
Knowledge Assessment Failures	10%	4%

The TRIG states that a single pharmacy may be pending enrollment for more than one reason. The primary reason for pending enrollments is "pending test transaction verification" although "no attestation" and "training not complete" were frequent causes as well. The TRIG does not provide additional detail as to why these reasons would extend for so long a period of time.

Wholesaler/Distributor Enrollment:
During the current reporting period, 1 (4.8%) wholesaler/distributor was newly enrolled in the REMS program and 20 (95.2%) re-enrolled. There were 5 wholesalers/distributors inactivated during the current reporting period due to enrollment expiration and 3 had not re-enrolled by the end of the reporting period because they were acquired by other enrolled entities or were initially enrolled as the wrong stakeholder type.

5.1.1. Reviewer Comments:

1. The number of newly enrolled patients this reporting period decreased by over 50% as compared to the previous reporting period, while the number of enrolled prescribers decreased by 10% this reporting period as compared to the last.
2. Of the 3,616 prescribers whose enrollment expired at some point during the current reporting period, 2,763 (76.4%) remained expired at the end of the reporting period. Similarly, Of the 4,530 pharmacies inactivated this reporting period, 57.6% (2,610) remained inactivated at the end of the reporting period. The reasons for inactivation were 0.7 – 7.4% due to "program opt out" and 93-99% due to "enrollment expired."

   In the FDA's 36-month RAAL, the TRIG was asked to "*Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues.*" In the 48 month assessment report, the TRIG responded that: "*Based on…analysis, there is no barrier to patient access and further outreach is unwarranted*." The TRIG stated that 8.6% of prescribers who chose to not re-enroll had an average of no more than four prescriptions total over the course of the reporting period. However, the reasons why the remaining prescribers did not re-enroll in the program were not addressed, and the reasons why many pharmacies did not re-enroll were similarly unknown. Additionally, the reasons why 412 pharmacies chose not to re-enroll are not presented. Thus in the 48-month RAAL the TRIG was told that they should conduct an *"…outreach to a representative sample of those health professionals and*

pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons…(w)e are concerned about potential patient access issues." The TRIG was told to submit a timeline for the outreach plan in the February 17, 2017, submission of the supplemental 60-month REMS assessment.

In the February 17, 2017 Supplement to Assessment report submission, the TRIG stated that they have ": *"In response to the request from the FDA, a timeline has been developed to perform outreach to a representative sample of those health professional and pharmacies that did not re-enroll in the TIRF REMS Access program to ascertain their reasons for not re-enrolling. The TRIG has initiated activities to collect these data and results will be included in the 72-Month FDA REMS Assessment Report*."

Additionally, the Agency's April 28, 2017 IR to the TRIG requested that they "*…develop an opt-out form that includes various opt-out reasons that are mutually agreed upon by the Agency and the TRIG…The TRIG would provide this form to the stakeholder to complete and submit to the REMS as written confirmation of their intention to opt-out of the program.*" On May 30, 2017, the TRIG responded that their outreach activities to stakeholders who do not re-enroll **"***…will only include those who were deactivated for failure for re-enrollment (lapse in enrollment based on lack of action of the prescriber), not those who opt-out of the program (proactive communication to the program to have enrollment end). The TRIG can collect information via an opt-out form for stakeholders, but it is unclear whether any useful data will be obtained as collection of opt-out reasons would require proactive outreach of a stakeholder that is not interested in participating in the program.*"

The Agency looks forward to reviewing the data in the 72-month Assessment Report as to the reasons why those who chose not to re-enroll. As part of the data to be submitted for the 72-month report, the TRIG will be asked to investigate whether pharmacy inactivations occurred disproportionately among any particular chain or geographic region.

3. Chain pharmacies make up the vast majority (88.5%) of pharmacy types in the TIRF REMS program, and independent pharmacies comprise only 9.6%. While 48% of the chain stores that became inactivated this reporting period remained inactivated at the end of the reporting period, 77% of independent stores that became inactivated this reporting period remained so at the close of the period. During the previous reporting period, a similar pattern was shown in which a smaller proportion of inactivated chain stores remained inactive at the end of the reporting period (16.6%) as compared to independent pharmacies (78.4%). It is not clear why this large discrepancy

exists. Also, as can be seen in Tables 5, 7, and 8, independent pharmacies appear to receive more TIRF prescriptions than chain pharmacies. The TRIG will be asked to explain why there is a lower number of re-enrollments by independent pharmacies.

5.2. ASSESSMENT ELEMENT 2: DISPENSING

The second element of the Assessment Plan states:

2. *Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)*
    a. *Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity;*
    b. *Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken);*
    c. *Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons;*
    d. *Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized*
    e. *Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF;*
    f. *Number of prescriptions dispensed after ten days without a PPAF in place."*

In the TRIG's May 31, 2017 response to the FDA's April 28, 2017 IR,[3] the TRIG states that "***10,450*** *patients were dispensed a prescription for a TIRF during this reporting period…."* However the TRIG also stated that they are further researching this number to insure it represents unique patients only.

Table 5 (adapted from the TRIG's Table 13) summarizes unique prescriptions presented for dispensing, unique prescriptions that did not encounter any REMS rejections, and dispensing by type of pharmacy:

[3] The April 28, 2017 FDA IR asked the TRIG to provide us with how many patients were dispensed a prescription for a TIRF during this reporting period.

Table 5: Prescriptions from Outpatient Pharmacies That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing

	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b,c] 28DEC2011 to 28OCT2016		
Parameter	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Number of Unique Prescriptions Submitted for Authorization	117,335	373	117,708	675,373	3,408	678,781
Total Number of Unique Prescriptions That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing[a]	104,748 (89.3%)	328 (87.9%)	105,076 (89.3%)	602,101 (89.2%)	2,741 (80.4%)	604,842 (89.1%)
Independent Pharmacies	67,353 (57.4%)	N/A	67,353 (57.2%)	396,356 (58.7%)	N/A	396,356 (58.4%)
Chain Pharmacy Stores	37,395 (31.9%)	N/A	37,395 (31.8%)	205,745 (30.5%)	N/A	205,745 (30.3%)
Closed System Pharmacies	N/A	328 (87.9%)	328 (0.3%)	N/A	2,741 (80.4%)	2,741 (0.4%)

[a] Prescriptions successfully adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or cash bin (bin number).

[b] Percentages are based on the total number (N) of unique prescriptions that never encountered a REMS-related rejection for the reporting period.

[c] Includes authorizations from all pharmacies that were enrolled in the TIRF REMS Access program at any time from inception of the program.

Of the 117,708 unique prescriptions (closed and non-closed systems) submitted for REMS authorization, 89% did not encounter any REMS-related rejections (i.e., were authorized for dispensing by insurance or cash bin). Last reporting period, 152,686 prescriptions were submitted for authorization. Thus, the volume of TIRF prescriptions submitted for authorization decreased by 23% from the previous reporting period to this reporting period.

Approximately 64% of the prescriptions submitted for REMS authorization that did not encounter any REMS-related rejections were filled at independent pharmacies versus 36% from chains. Recall that independent pharmacies comprise only 9.6% of pharmacies enrolled in this REMS.

The TRIG presents data regarding prescriptions that either encountered at least one REMS-related rejection or were totally rejected due to REMS criteria. The TRIG has provided definitions for the reasons they cite for rejections and these are presented in **Table 6** below (reproduced in its entirety from the assessment report's Table 14):

Table 6 Reasons for Prescriptions Not Meeting REMS Requirements

Reason	Description
Prescriber Identification (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
Prescriber ID Not Registered	Found the prescriber last name but the NPI, DEA or State License Number does not match prescriber.
PPAF Expired	Patient's PPAF expired due to 2 year PPAF expiration
PPAF No Activity	Patient's PPAF has expired due to no transaction activity within past 6 months
PPAF Terminated	Patient's PPAF terminated due to 2 year PPAF expiration (status was replaced with PPAF Expired effective 17 March 2015)
Prescriber Terminated	Prescriber enrollment terminated
Pharmacy Terminated	Pharmacy enrollment terminated

Table 7 below (data extracted from the TRIG's Table 15) presents the number of outpatient prescriptions that **encountered at least one REMS-related rejection** prior to being authorized for dispensing as well as the most common reasons for the REMS rejection per pharmacy type:

Table 7: Prescriptions from Outpatient Pharmacies That Encountered at Least One REMS-Related Rejection Prior to Being Authorized for Dispensing

Parameter	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b c] 28DEC2011 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Number of Unique Prescriptions Presented for Dispensing	117,335	373	117,708	675,373	3,408	678,781
Total Number of Unique Prescriptions that encountered At Least One Initial REMS-Related Rejection Prior to being Authorized for Dispensing[a]	2,362 (2.0%)	1 (0.3%)	2,363 (2.0%)	21,733 (3.2%)	58 (1.7%)	21,791 (3.2%)
Independent Pharmacies	1,212 (1.0%)		1,212 (1.0%)	15,274 (2.3%)		15,274 (2.3%)
Chain Pharmacies	1,150 (1.0%)		1,150 (1.0%)	6,459 (1.0%)		6,459 (1.0%)
Closed System Pharmacies		1 (0.3%)	1 (<0.1%)		58 (1.7%)	58 (<0.1%)
Independent Pharmacies: Reason(s) for Rejection[d]						
Zip Code Missing	125 (10.3%)			6,689 (43.8%)		
PPAF Incomplete	319 (26.3%)			4,416 (28.9%)		
Prescriber last name did not match registered	79 (6.5%)			1,925 (12.6%)		
Prescriber ID not registered	139 (11.5%)			1,768 (11.6%)		
PPAF Expired	262 (22.8%)			1,102 (7.2%)		
PPAF terminated	0			884 (5.8%)		
Chain Pharmacies: Reason(s) for Rejection[d]						
PPAF Incomplete	178 (15.5%)			2,492 (38.6%)		
Prescriber ID not registered	104 (9.0%)			1,190 (18.4%)		
Zip Code Missing	181 (15.7%)			1,043 (16.1%)		
Prescriber last name did not match registered	425 (37.0%)			931 (14.4%)		
PPAF Expired	45 (9.4%)			656 (10.2%)		
PPAF terminated	0			518 (8.0%)		
Closed System: Reason(s) for Rejection[d]						
Zip Code Missing		0		33 (56.9%)		
PPAF Incomplete		0		10 (17.2%)		
Prescriber ID not registered		0		9 (15.5%)		
PPAF terminated		0		6 (10.3%)		
Prescriber last name did not match registered		0		6 (10.3%)		
PPAF Expired		0		3 (5.2%)		
PPAF No Activity		1 (100.0%)		1 (1.7%)		

a Prescription successfully adjudicated for safety (i.e., successful REMS edit).and authorized for dispensing by insurance or cash bin (bin number).

b Percentages are based on the total number (N) of number of unique prescriptions that encountered at least one initial REMS-related rejection prior to being authorized for dispensing for the reporting period.

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

d Prescriptions can be rejected for more than one reason.

The TRIG also states that the percentages for all rejection reasons in the following tables may not equal 100% as a prescription may be rejected for multiple reasons

A total of 2,362 of (non-closed system) prescriptions (or 2% of the overall number of prescriptions submitted for REMS authorization) received at least one REMS-related rejection prior to dispensing. The total number of rejections was quite similar between chain and independent pharmacies although the overall volume of prescriptions submitted by independent pharmacies for authorization is higher than the overall volume for chains.

The reasons for rejection between chains, independents, and closed systems were similar and involved either some form of an incomplete PPAF or a prescription written by a non-registered prescriber.

Table 8 below (data extracted from the TRIG's Table 16) presents the number of outpatient prescriptions that encountered at least one REMS-related rejection prior and were never authorized for dispensing as well as the most common reasons for the REMS rejection per pharmacy type:

Table 8: Prescriptions That Encountered at Least One REMS-Related Rejection and Were Never Authorized for Dispensing

Parameter	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b c] 28DEC2011 to 28OCT2016		
	Non-Closed System	Closed System	All Pharmacies	Non-Closed System	Closed System	All Pharmacies (Non-Closed
Number of Unique Prescriptions Presented for Dispensing	117,335	373	117,708	675,373	3,408	678,781
Total Number of Unique Prescriptions that encountered At Least One Initial REMS-Related Rejection Prior to being Authorized for Dispensing[a]	10,225 (8.7%)	44 (11.8%)	10,269 (8.7%)	51,539 (7.6%)	609 (17.9%)	52,148 (7.7%)
Independent Pharmacies	3,386 (2.9%)		3,386 (2.9%)	23,849 (3.5%)		23,849 (3.5%)
Chain Pharmacies	6,839 (5.8%)		6,839 (5.8%)	27,690 (4.1%)		27,690 (4.1%)
Closed System Pharmacies		44 (11.8%)	44 (<0.1%)		609 (17.9%)	609 (0.1%)
Independent Pharmacies: Reason(s) for Rejection[d]						
Prescriber ID not registered	1,105 (32.6%)			10,770 (45.2%)		
Prescriber last name did not match registered	432 (12.8%)			4,328 (18.1%)		
Zip Code Missing	631 (18.6%)			2,985 (12.5%)		
Prescriber is terminated	778 (23.0%)			2,468 (10.3%)		
PPAF Incomplete	168 (5.0%)			2,459 (10.3%)		
Chain Pharmacies: Reason(s) for Rejection[d]						
Prescriber ID not registered	1,298 (19.0%)			14,870 (53.7%)		
Prescriber last name did not match registered	3,711 (54.3%)			6,163 (22.3%)		
PPAF Incomplete	139 (2.0%)			2,482 (9.0%)		
Prescriber is terminated	592 (8.7%)			2,019 (7.3%)		
Zip Code Missing	1,393 (20.4%)			1,759 (6.4%)		
Closed System: Reason(s) for Rejection[d]						
Prescriber ID not registered		23 (52.3%)		330 (54.2%)		
Prescriber last name did not match registered		8 (18.2%)		111 (18.2%)		
PPAF Incomplete		0		55 (9.0%)		
Pharmacy is terminated		6 (13.6%)		47 (7.7%)		
Prescriber is terminated		4 (9.1%)		38 (6.2%)		

A total of 10,225 non-closed system prescriptions (8.7% of the total amount of prescriptions submitted for REMS authorization) were never authorized for dispensing due to REMS-related rejections. Over twice as many chains as compared to independents experienced such events even though the volume of overall prescriptions submitted for authorization by chains was less than the volume submitted by independents. The primary reason for rejection for all pharmacy types was due to a prescription written by a non-registered prescriber.

Prescription Authorization Times

Table 9 below (taken in part from the TRIG's Report Table 17) presents the mean and median times to eventual prescription authorization after the prescription experienced at least one REMS-related rejection per pharmacy type:

Table 9: Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection

	60 month Reporting Period 29OCT2015 to 28OCT2016	**48 month** Reporting Period 29OCT2014 to 28OCT2015	**36 month** Reporting Period 29OCT2013 to 28OCT2014	**24 month** Reporting Period 29OCT2012 through 28 OCT2013	**Cumulative** 28DEC2011 to 28OCT2015
Total Mean Time For Prescription to be Authorized[a] (Days)[b]	6.30	6.68	4.90	2.10	**4.02**
Inpatient Pharmacies	--	--	--		--
Chain Pharmacy Stores	7 14	7 81	5 10		**4.93**
Independent Outpatient Pharmacies	5 46	6 25	4 82		**3.62**
Closed System Pharmacies	56 86[c]	--	10 04		**7.16**
Total Median Time For Prescription to be Authorized[a] (Days)[b]	2.03	1.32	1.06	0.01	**0.70**
Inpatient Pharmacies	--	--	--		--
Chain Pharmacy Stores	2 80	2 17	1 73		**1.17**
Independent Outpatient Pharmacies	1 68	1 03	0 98		**0.15**
Closed System Pharmacies	56 86[c]	--	2 48		**1.16**

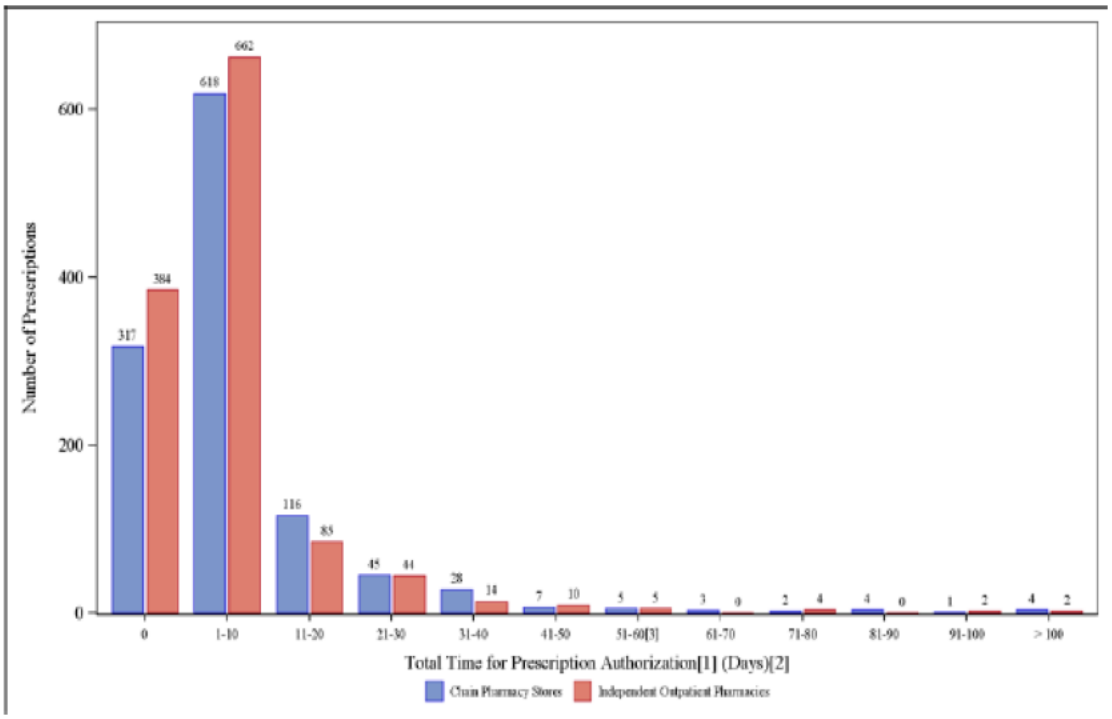
a Prescriptions included were resolved in the current reporting period. Prescriptions may have been initially rejected in a previous reporting period.
b Time to authorization for a prescription that experienced at least one initial REMS-related rejection excludes prescriptions processed through the inpatient pharmacy process.
c The mean and median data represent the actual time to authorization for 1 closed system pharmacy prescription..

The median prescription processing time for a prescription that experienced at least one initial REMS-related rejection appears to continue to increase over time for both chain and independent stores.

In both the 36-month and the 48-Month FDA RAALs, the FDA requested that the TRIG investigate the cause of increasing delays in prescription processing since these may be potential indicators of access barriers. The TRIG did not submit the results of such an investigation. However, in the current report, the TRIG did provide data indicating that of all the prescriptions that encounter at least one REMS-related rejection over 80% are resolved within the first 10 days. The TRIG also commented that "*At the current time it is not possible to distinguish between prescriptions that encounter at least one REMS-related rejection that are quickly resolved and those that are not*."

Figure 1 below (reproduced from the TRIG Assessment Report's Figure 1) shows the distribution of time to authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection during the current reporting period.

Figure 1: Distribution of Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection for the Current Reporting Period



Closed Systems:

The six closed-system pharmacy entities enrolled in the TIRF REMS Access program during this reporting period are listed below:

- (b) (4) (b) (4)
- National Institutes of Health Clinical Center Pharmacy
- U.S. Department of Veterans Affairs
- (b) (4) (b) (4) (b) (4) (b) (4)
- DLA Troop Support
- (b) (4) (b) (4)

Table 10 below (adapted from the TRIG's Table 19) lists the number of prescription authorizations for each closed system entity:

Table 10: Number of Prescription Authorizations per Closed System Pharmacy for the Current Reporting Period and Cumulatively

	Current Reporting Period 29OCT2015 to 28OCT2016	48 month Reporting Period 29OCT2014 to 28OCT2015	36 month Reporting Period 29OCT2013 to 28OCT2014	Cumulative 28DEC2011 to 28OCT2016
Total Number of Closed System Pharmacy Prescription	329	398	730	2,799
(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	(b) (4)			
Veterans Affairs	52 (15.8%)	26 (6.5%)	51 (7.0%)	212 (7.6%)
DLA Troop Support	21 (6.4%)	29 (7.3%)	35 (4.8%)	101 (3.6%)
(b) (4) 4)	(b) (4)			
National Institutes Of Health	0	0	1 (0.1%)	4 (0.1%)

Cumulatively, (b) (4) (b) (4)) (4) (b) (4) (b) (4) account for 71% of the 2,799 closed system prescriptions authorized. The listed governmental entities account for a cumulative total of 4% of the closed system prescriptions authorized.

During the previous reporting period, (b) (4) transitioned from being a closed-system pharmacy to a non-closed system pharmacy. Thus the prescription authorizations described in Table 18 for (b) (4) only represent prescriptions processed prior to this transition.

The 36-month REMS Assessment Acknowledgement Letter requested that the TRIG "*Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report.*" In their 48-month Assessment Report, the TRIG stated that the current prescription authorization volume for closed system pharmacies is <1% of all TIRF prescriptions and that these types of pharmacies account for <1% of all pharmacies enrolled in the REMS. Additionally, the TRIG stated that no complaints had been received from the closed system pharmacies regarding REMS processes and thus *"...no changes are warranted at this time.*"

In the current Assessment Report, while the TRIG acknowledges that there have been non-compliance events identified through closed system audits (where REMS

processes have been bypassed), the TRIG lists several challenges in working with closed system pharmacies:

- the transient nature of pharmacy staff at these locations
- some locations are unable to access outside websites

PPAF data

Table 11 below (taken directly from the Assessment Report's Table 20) summarizes the number of prescriptions dispensed during the first 10 days with and without a PPAF:

Table 11: Prescriptions Dispensed During the First 10 Days With and Without a PPAF

	Current Reporting Period 29OCT2015 to 28OCT2016				Cumulative[a] 28DEC2011 to 28OCT2016			
Parameter	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Combined Pharmacies[d] N (%)	Total Pharmacies N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Combined Pharmacies[d] N (%)	Total Pharmacies N (%)
Number of prescriptions dispensed during the first 10 days after patient enrollment	3,259	11	0	3,270	40,727	222	11	40,960
Number of patients dispensed a prescription during the first 10 days after enrollment	2,817	11	0	2,828	34,061	185	5	34,251
With PPAF[b]								
1 Fill	1,597 (56.7%)	4 (36.4%)	0	1,601 (56.6%)	14,978 (44.0%)	57 (30.8%)	1 (20.0%)	15,036 (43.9%)
2 Fills	246 (8.7%)	0	0	246 (8.7%)	2,872 (8.4%)	9 (4.9%)	0	2,881 (8.4%)
3 Fills	38 (1.3%)	0	0	38 (1.3%)	423 (1.2%)	1 (0.5%)	0	424 (1.2%)
>3 Fills	6 (0.2%)	0	0	6 (0.2%)	86 (0.3%)	2 (1.1%)	0	88 (0.3%)
Without PPAF[b,c]								
1 Fill	922 (32.7%)	7 (63.6%)	0	929 (32.9%)	14,855 (43.6%)	107 (57.8%)	1 (20.0%)	14,963 (43.7%)
2 Fills	50 (1.8%)	0	0	50 (1.8%)	1,384 (4.1%)	5 (2.7%)	3 (60.0%)	1,392 (4.1%)
3 Fills	3 (0.1%)	0	0	3 (0.1%)	225 (0.7%)	4 (2.2%)	1 (20.0%)	230 (0.7%)
>3 Fills	0	0	0	0	10 (<0.1%)	0	0	10 (<0.1%)

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

The REMS states that the TRIG is to monitor prescribers' compliance with the requirement to complete a PPAF with each TIRF patient, and to submit it to the REMS within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No

further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. The TRIG also points out that a patient could receive both prescriptions without and then with a PPAF in the first 10 days depending on when the PPAF was filled out and thus the patient numbers likely contain some duplications.

For this reporting period, during the first 10 days, from ALL pharmacies, 3,270 prescriptions were dispensed during the first 10 days after patient enrollment totaling 2,828 patients. Of these patients:

- The majority of patients (n=2,817) were dispensed prescriptions by non-closed system pharmacies (3,259 prescriptions)
- 56.7% of patients had one prescription filled **with** a PPAF
- 32.7% of patients had one prescription filled **without** a PPAF
- 1.9% of patients had either 2 or 3 prescriptions fills without a PPAF
- NO patient had more than 3 fills without a PPAF
- NO prescriptions were dispensed beyond 10 days after enrollment without a PPAF

From the inception of the TIRF REMS through the current reporting period, 751 prescriptions from non-closed systems and 32 prescriptions from closed systems (data not presented) have been dispensed beyond the first 10 days without a PPAF (although none this reporting period).

5.2.1. Reviewer Comments

1. The volume of TIRF prescriptions submitted for authorization decreased by 23% from the previous reporting period to this reporting period.

2. Approximately 64% of the prescriptions submitted for REMS authorization that did not encounter any REMS-related rejections were filled at independent pharmacies versus 36% from chains. However, independent pharmacies comprise only 9.6% of pharmacies enrolled in this REMS. In the Agency's April 28, 2017 IR to the TRIG, the Agency asked the TRIG to provide insight into why these independent pharmacies dispense the bulk of TIRF prescriptions. In the TRIG's May 30, 2017 response, they state that *"…the TIRF REMS Access program does not require the collection of pharmacy sub-type, so the TRIG is unable to provide an evidence-based rationale for this observation.*" Given the small market share that TIRF products occupy, the TRIG should be able to provide additional perspective regarding this question.

   In addition, the TRIG states that their "independent pharmacy" category contains "*retail, mail order, and institutional outpatient pharmacies*." For subsequent assessments, the TRIG will be asked to specify what proportion of prescriptions comes from which sub-category of independent pharmacies.

3. The median prescription processing time for a prescription that experienced at least one initial REMS-related rejection appears to continue to increase over time for both chain and independent stores. In the Agency's April 28, 2017 information request to the TRIG, the Agency noted that our 36-month and 48-month RAALs pointed out these increasing processing times for prescriptions experiencing at least one REMS-related rejection and urged the TRIG to investigate and identify the causes of these increasing delays. The Agency also pointed out that since the reasons for REMS-related rejections (PPAF incomplete, PPAF not submitted, prescriber not registered) appear to have remained the same over time, the TRIG should further explore this increase in processing times by evaluating a sample of the prescription rejections with the longest processing time to determine if there are any identifiable reasons for this that could be addressed in the REMS.

   In the 60-month assessment report, the TRIG provides data that shows that of all the prescriptions that encounter at least one REMS-related rejection, over 80% are resolved within the first 10 days. The TRIG also commented that "*At the current time it is not possible to distinguish between prescriptions that encounter at least one REMS-related rejection that are quickly resolved and those that are not*."

   In the TRIG's May 30, 2017 response to the Agency's April 28, 2017 information request, the TRIG states only that "*…data are not available to be able to determine which prescriptions…are driving the increase in time to authorization…Further, there may be variables outside of those described…that may impact the mean and median time for a prescription to be authorized.*"

   In response to issues raised at the October 2, 2017 telecon between the FDA and TRIG, on October 16, 2017, the TRIG stated that they plan "*…to conduct an analysis of prescription processing times for prescriptions that encounter at least one REMS-related rejection over the period October 29, 2014 – October 28, 2017 to evaluate trends over time. In addition to this analysis, TRIG will expand the reporting of these data to FDA to show a more holistic view of overall REMS rejections, which will put into context the overall processing time for all rejected TIRF prescriptions. The updated metrics will be included in the 02FEB2018 submission.*"

   In such an analysis that the TRIG stated on October 16, 2017 that they plan to conduct, the TRIG needs to clarify whether their use of the term "authorization" is limited to REMS authorizations or dispensing authorizations, since the latter may reflect insurance issues. For patients who were denied a TIRF prescription due to a missing or incomplete PPAF, it is

unclear in how many instances did the prescriber complete the PPAF versus simply prescribe an alternative therapy. The TRIG will be asked to provide any data informing this issue since this may be an indicator of a potential access issue.

5.3. ASSESSMENT ELEMENT 3: PROGRAM INFRASTRUCTURE

The third element of the Assessment Plan states:

3. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

- *a. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described;*
- *b. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions;*
- *c. Call center report with:*
  - *i. Overall number of contacts;*
  - *ii. Summary of frequently asked questions;*
  - *iii. Summary of REMS-related problems reported*
- *d. Description of corrective actions taken to address program/system problems.*

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.

Of the 124,796 calls to the TIRF REMS Call Center received during this reporting period, the reasons reported for 82% of the calls were: enrollment status inquiry (17%); pharmacy calls for pharmacy claim rejection (16%); PPAF inquiry (10%), and general program questions (6%). The TRIG states that there were no REMS-related barriers reported to the REMS Call Center during this reporting period.

5.4. ASSESSMENT ELEMENT 4: PROGRAM NON-COMPLIANCE

The fourth element of the Assessment Plan states:

4. TIRF REMS Access Non-Compliance Plan: The TIRF TRIGs should provide the following data regarding non-compliance in each assessment report (per reporting period):

a. *Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:*

i. *Verification of training for all pharmacists dispensing TIRF products;*

ii. *Numbers of prescription authorizations per closed system;*

iii. *Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS program period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).*

iv. *Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance*

b. *Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period. These reports are to include:*

v. *Verification of training for all pharmacists dispensing TIRF products*

vi. *Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program*

vii. *Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events*

c. *Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:*

viii. *Description of how the NCRT defines a non-compliance event*

ix. *Description of how non-compliance information is collected and tracked*

x. *Criteria and processes the Team uses to make decisions*

xi. *Summary of decisions the Team has made during the reporting period*

xii. *How the Team determines when the compliance plan should be modified*

d. *Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action*

e. *Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrence*

f. *Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences*

g. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified

h. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified

i. *Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified.*

Table 12 below (taken in its entirety from the assessment report's Table 24) summarizes non-compliance reports by stakeholder during the current reporting period.

Table 12: Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period

Stakeholder[a]	Non-Compliance Activity	Non-Compliant Reason (categorized as reported by the stakeholder)	No. of events	No. of stakeholders
Non-Closed System Pharmacy	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF PMS that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Not aware of requirement to process cash claims	3	No. w/1 report: 3
		Received reject but dispensed drug	2	No. w/1 report: 2
		Dispensed drug without obtaining an authorization	2	No. w/1 report: 2
		Total Non-Closed System Pharmacy Cases	7	
Wholesaler/Distributor	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.	No reason provided	1	No. w/1 report: 1
		Total Wholesaler/Distributor Cases	**1**	
Prescriber	Prescriber failure to have a complete PPAF on file in a timely manner (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from the initial enrollment date).	Not aware of PPAF requirement	9	No. w/1 report: 9
		Completed PPAF with patient but failed to send PPAF to TIRF REMS	18	No. w/1 report: 18
		Aware of PPAF requirements but failed to complete PPAF	8	No. w/1 report: 8
		No reason provided	15	No. w/1 report: 15
		Total Prescriber Reports	**50**	
		Total Number of Reports During This Reporting Period	**58**	

[a] There were no spontaneous reports of non-compliance from closed-system pharmacies.

The TRIG states that the above table includes single noncompliance cases (as has been discussed in previous reviews, the TRIG's definition of a "single" compliance case for a PPAF in fact requires five such cases). The TRIG states that if the cases noted in this table appear for two consecutive assessment reports, such reports will not be placed into this table but be reported in narrative fashion only. The TRIG states that a total of 62 instances of potential stakeholder non-compliance with the TIRF REMS occurred this reporting period. Fifty-eight of these reports appeared in Table 13, whereas four reports were described in narrative fashion.

There were **50 cases** where a prescriber failed to have a complete PPAF on file in a timely manner (each case includes 5 or more patients enrolled by the prescriber

without a complete PPAF on file, with each patient having greater than 10 working days lapse from the initial enrollment date). Given that each case involved at least 5 PPAFs this means that a minimum of 250 PPAFs were not submitted in a timely fashion.

There were seven instances in which a TIRF prescription was dispensed because a pharmacy was able to bypass the REMS. A total of three of these seven instances were due to not using the cash BIN to process a claim. In all three of these instances the pharmacy was re-educated. In the remaining four instances:

- Two cases of a pharmacy the dispensed a TIRF without obtaining an authorization. The pharmacy was re-educated.
- Two cases of a pharmacy dispensing a TIRF after receiving a reject message that the prescriber certification had lapsed. The prescriber completed re-enrollment and the pharmacy was re-educated.

In the Agency's April 28, 2017 IR to the TRIG, the Agency asked the TRIG if, out of the 10,225 non-closed system prescriptions that were never authorized for dispensing due to REMS-related rejections, how many of these prescriptions were dispensed despite of the rejection. In the TRIG's May 30, 2017 response, they state that "*There is no way to systematically and accurately track if a pharmacy receives this rejection and still makes the decision to dispense*."

In the Agency's April 28, 2017 IR to the TRIG, the Agency also asked the TRIG, regarding the cases of the pharmacy not being aware of the need to process cash claims through the REMS or a pharmacy dispensing a TIRF without a REMS authorization, or a pharmacy receiving a reject through the REMS but dispensing the TIRF anyway, how is it that the TRIG learned of these cases. In the TRIG's May 30, 2017 response, they state that "*All of these referenced instances would only be captured through spontaneous reports to the TIRF REMS Access program*." Thus, under-reporting of events of non-compliance is quite likely.

Table 12 includes a case where a prescription was dispensed by a non-enrolled pharmacy that was shipped a TIRF from an enrolled distributor. The REMS was notified of this when the non-enrolled pharmacy contacted the TIRF REMS regarding a prescription rejection for reason of "pharmacy not enrolled". The non-enrolled pharmacy shipped the TIRF back to the distributor. The distributor was reeducated on the REMS requirements

Although Table 12 contains a footnote that "There were no spontaneous reports of non-compliance from closed-system pharmacies" the TRIG reports one instance where the Call Center incorrectly provided authorization for a closed system pharmacy to dispense the TIRF even though the prescription was written by non-enrolled prescriber. The prescriber was informed of the REMS requirements and the Call Center Staff was retrained.

The four narrative cases of non-compliance provided by the TRIG involve compliance events that occurred over a period of time.

- A prescriber was identified as not submitting PPAFs for "multiple" patients on three separate occasions. After the first two incidents, formal Notices for Non-Compliance were issued to the prescriber, but after the third incident the prescriber was issued a Warning Letter requiring that a compliance action plan (CAP) be submitted. The first CAP submitted by the prescriber was not approved by the NCRT, but a revised CAP was later accepted. The prescriber was once again issued a Warning Letter requiring that a CAP be submitted for non-submittal of PPAFs. The CAP was again accepted. A year and a half later the prescriber was identified as failing to submit PPAFs. After multiple attempts to contact the prescriber failed, the prescriber was issued another Warning Letter requiring that a CAP be submitted. After two unsuccessful CPA submissions, the third CAP was accepted by the NCRT.
- Another prescriber was identified as not submitting PPAFs for 6 patients on two separate occasions. After the second incident, a Warning letter was issued to the prescriber with a request for a CAP; however, the NCRT did not approve the CAP. After multiple unsuccessful attempts to reach the prescriber for a valid CAP, the prescriber was suspended from the TIRF REMS Access program. A CAP was received a month later and accepted by the NCRT and the prescriber was re-enrolled in the TIRF REMS program.
- A prescriber was identified as not submitting PPAFs for 5 patients on three separate occasions. After the first two incidents, formal Notices for Non-Compliance were issued to the prescriber, but after the third incident the prescriber was issued a Warning Letter requiring that a CAP be submitted. The first CAP submitted by the prescriber was not approved by the NCRT, but a revised CAP was later accepted.

Closed System Audits

The REMS Assessment Plan includes the following three components for closed system pharmacy audits:

1. Verification of training for all pharmacists dispensing TIRF products
2. Numbers of prescription authorizations per closed system
3. Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access program

The first component of the closed system pharmacy audit requirement is accomplished through the enrollment process for the pharmacy. To become enrolled, the authorized representatives must attest that all pharmacy staff that

participate in dispensing TIRF products will be trained on the TIRF REMS Access program requirements. The second component is done through the closed system pharmacy prescription authorization process. Closed system pharmacists are required to validate the enrollment status of the prescriber and patient prior to dispensing a TIRF product by calling or faxing the prescription details to the TIRF REMS Access program.

Regarding this third component, the TRIG describes that the process of reconciliation between the closed system pharmacy's dispensing data and the REMS program's authorizations necessitates the TRIG requesting dispensing records from the closed system pharmacies and compares these records to the TRIG's authorization data. After confirmation that the closed system pharmacy agrees to participate in the audit, a formal written request for data is issued upon request to the authorized representative detailing the data to be provided and the deadline for submission. Specific data requested include:

- RX number for each prescription dispensed
- DEA number or NPI number of the facility that dispensed each prescription
- DEA number or NPI number of the prescriber that issued each prescription
- Date and time of each prescription transaction
- REMS Authorization code obtained for each prescription dispensed

The TRIG states that due to the structure of some closed system pharmacies, their headquarters may be unable to provide data for all pharmacy locations as no central data repository is in existence (each pharmacy location maintains their own data). In these cases a random sample of pharmacy locations was selected for participation by the TRIG. Findings from each investigation are reviewed with the NCRT and actions were taken in accordance with the Non-Compliance Protocol. The TRIG states that the REMS assessment metric for closed system audits requires auditing of at least 3 randomly selected closed system pharmacies. The TRIG however included all closed-system pharmacies in the audit with a request to provide dispensing records from May 1, 2015 through April 30, 2016.

Table 13 below (copied in its entirety from the assessment report's Table 26) summarizes the reconciliation of the dispensing data from each closed system pharmacy and the authorizations received from the TIRF REMS program for the six audited closed system pharmacies:

Table 13: Results of the Closed System Pharmacy Audits

Audit ID Number	Date Closed System Monitoring Request for Data Sent	Date Dispensing Records Received[1]	Total Dispenses/Total Dispenses Not Authorized by the REMS	Non-Compliance Identified?
1 (ID#CS7)	26 May 2016	08 July 2016	164/1	Y
2 (ID#CS8)	26 May 2016	15 June 2016[2]	0/0	N
3 (ID#CS9)	26 May 2016	07 September 2016	40/7	Y
4 (ID#CS10)	26 May 2016	02 September 2016	27/1[3]	Y
5 (ID#CS11)	26 May 2016	20 June 2016[2]	0/0	N
6 (ID#CS12)	26 May 2016	02 September 2016	99/59	Y

[1] The date range for dispensing records received was 01 May 2015 through 30 April 2016.

[2] Pharmacy provided confirmation that no TIRF medicines were dispensed during the reporting period (01 April 2014-30 April 2015).

[3] Initial data showed that there was one location with three instances of dispensing TIRF medications without an authorization. However, after issuance of a Notice for Non-Compliance, additional information was received from the pharmacy confirming that the one location only had one instance of dispensing TIRF medications without an authorization.

Of the 6 audits conducted during this reporting period, 4 closed system pharmacies (ID#CS7 [(b) (4) (b) (4) ID#CS9 [VA], ID#CS10 [(b) (4) (b) (4) and ID#CS12 [DoD]) were found to be non-compliant with the TIRF REMS Access program requirements. A non-compliance case was opened for each of these 4 closed systems.

- **ID#C57 (**(b) (4) (b) (4) - For the one unauthorized dispensation out of 164, a second formal Notice for Non-Compliance was issued requiring a CAP which was subsequently approved by the TRIG.
- **ID#CS9 (Veterans Administration [VA])** – since the VA has no central document system, TIRF REMS Access program provided 8 randomly selected and enrolled VA closed-system dispensing locations (accounting for 10% of the enrolled population for VA), out of 40 VA system authorizations, 1 location had 7 instances of dispensing TIRF medications without authorization. A third formal Notice for Non-Compliance was issued and a CAP was initiated. The system used at the pharmacies was updated to add a reminder for each TIRF NDC that authorization was required for dispensing and a Standard Operation Procedure (SOP) was developed to define the need for prior authorization. This CAP was approved by the NCRT.
- **ID#CS10 (**(b) (4) (b) (4) (b) (4) – (b) (4) requested that the TIRF REMS program provided REMS authorization data for randomly selected sites and provide the information to (b) (4) which would then reconcile their own pharmacy's data to identify any non-compliance. The audit revealed one

unauthorized dispensation out of 27 dispensations. A second formal Notice for Non-Compliance for was issued requiring a CAP. The NCRT approved the CAP.

- **ID#CS12 (Department of Defense [DoD])** – the DoD requested that the TIRF REMS Access program provide REMS authorization data from the TIRF REMS Access program so that they could match it to their pharmacy data. The audit data showed that 11 locations had 59 instances of dispensing TIRF medications without authorization (out of 99 dispensation audited). Of the 11 locations, 3 locations were not enrolled in the TIRF REMS Access program. A third formal Notice for Non-Compliance for was issued requiring a CAP. Future plans have been made to conduct ongoing quarterly educational sessions to inform the military treatment facility on the REMS requirements until understanding, awareness, and compliance is stable. The NCRT approved the CAP.

The TRIG is evaluating is quarterly review of closed system pharmacy data rather than an annual review in the current audit process.

Inpatient Pharmacy Audit

The inpatient hospital pharmacy audit process is conducted through an audit questionnaire invitation that is faxed to authorized inpatient pharmacists of pharmacies enrolled in the TIRF REMS Access program requesting their participation. Once the authorized inpatient pharmacist agrees to participate, they receive the audit questionnaire. If the authorized pharmacist replies that they are indeed a hospital pharmacy and have dispensed a TIRF in the previous 12 months, they are then asked the following:

1. *Provide the number of units dispensed within <insert date range>. (See NDC list for a current listing of TIRF NDCs) _____units of use of TIRFs dispensed to inpatients.*
2. *Did all pharmacists who dispensed TIRF medicines complete training on the TIRF REMS Access program prior to dispensing these products? Yes/No*
3. *Do you have procedures in place such as order sets/protocols to assure compliance with the TIRF REMS program requirements? Yes/No. If yes, are you willing to provide examples of an order set or protocol?*

A total of 12 enrolled inpatient locations were solicited for participation in the audit:

- 3 did not respond to the audit invitation
- 4 pharmacies answered that they were either not a hospital inpatient pharmacy facility or had not dispensed TIRFs in the previous 12 months.

The remaining 5 qualified to participate in the audit, and proceeded to respond to the 3 audit questions listed above. Based on responses to the 3 audit questions, 4 of

the 5 audited inpatient hospital pharmacies were found to be compliant with the REMS program requirements. One inpatient hospital pharmacy was found to be non-compliant and a non-compliance case was opened:

- The inpatient pharmacy reported dispensing 7 units of TIRFs in the previous 12 months, but also admitted that the pharmacists who dispensed these TIRFs had not completed training on the REMS program prior to dispensing these products. A Warning Letter was issued to the pharmacy requesting a CAP. The CAP was subsequently received and stated that all pharmacists would complete REMS training. The NCRT approved the CAP. The TRIG plans to invite the same pharmacy to participate in the audit in 2017.

5.4.1. Reviewer Comments

1. Concerns about the TRIG's REMS overall compliance program continue and include the following issues:
   a. For the 60-month report, the TRIG continued to classify a case of PPAF non-compliance as **Five** or more patients enrolled by the prescriber without a complete PPAF on file (greater than 10 working days from the initial enrollment date not on file with the REMS). In the 48-month RAAL, the TRIG was told of FDA's concern that these criteria could lead to an under-reporting of PPAF non-compliance and that they should explore mechanisms to capture lower levels of non-compliance. The TRIG stated that they evaluated the occurrences of their definition of PPAF non-compliance (named "Prescriber 2 Scenario" by the TRIG) using the following denominators:
      - Prescribers enrolled as of the end of the reporting period;
      - total number of prescriptions submitted for authorization, and
      - total number of prescriptions that were authorized by the TIRF REMS

   The TRIG reported that the rates of this non-compliance scenario across all denominators have gradually decreased from the 36-month reporting period to the current reporting period (see **Table 14** below, taken from the assessment report Table 23).

Table 14: Rates of Prescriber 2 Scenario Cases Over Time

	36-Month FDA REMS Assessment Report (N=120 reports)	48-Month FDA REMS Assessment Report (N=82 reports)	60-Month FDA REMS Assessment Report (N=50 reports)
Per 1,000 prescribers[a]	15.02	9.01	6.13
Per 10,000 submitted prescriptions[b]	7.52	5.37	4.25
Per 10,000 authorized prescriptions[c]	8.06	5.64	4.65

[a] The prescriber rates were based on reported number of prescribers enrolled as of the end of the reporting period. The denominators used for the 36-Month, 48-Month, and 60-Month REMS Assessment Report calculations were 7,992; 9,096; 8,151.

[b] The submitted prescription rates were based on the total number of prescriptions submitted for authorization. The denominators used for the 36-Month, 48-Month, and 60-Month REMS Assessment Report calculations were 159,560; 152,686; 117,708.

[c] The authorized prescription rates were based on the number of prescriptions that did not encounter any REMS-related rejections and was dispensed and the prescriptions that encountered at least one REMS-related rejection, but were eventually authorized and dispensed. The denominators used for the 36-Month, 48-Month, and 60-Month REMS Assessment Report calculations were 148,822; 145,498; 107,439.

Thus the TRIG determined that this established non-compliance definition is working and that they would continue to explore mechanisms to capture lower instances of non-compliance.

These data do appear to indicate that occurrences of their definition of PPAF non-compliance appear to be decreasing. However, lower levels of prescriber non-compliance (<5 PPAFs not submitted to the REMS in a timely manner) are not captured. Thus the overall level of PPAF non-compliance remains unknown. It is also unknown whether or not the bulk of PPAF non-compliance is actually caused by prescribers with these lower levels of non-compliance.

The TRIG was told of the FDA's continued concerns regarding needing 5 PPAFs to establish one case of non-compliance at the October 2, 2017 telecon. In response, on October 16, 2017, the TRIG stated the following: "*The TRIG will reduce the PPAF threshold to flag prescribers for non-compliance based on patients without a PPAF from 5 to 3 patients. The TRIG evaluated the incidents of non-compliance and has determined that the threshold can be lowered to 3 without a large impact to patient access.* "

Because the TRIG did not elaborate further how lowering the number of PPAFs needed for a case on non-compliance to less than 3 would affect

patient access, FDA sent another IR on October 27, 2017 asking for an explanation. In the TRIG's November 2, 2017 response, they state that: "*To determine the impact of decreasing the threshold for missing PPAFs triggering a non-compliant event, the TRIG calculated estimated increases in non-compliant case volume based on current prescriber and PPAF activity. At the time of this research, the TRIG found that lowering the threshold to:*

- *4 missing PPAFs would result in 2 additional non-compliant cases per month (~15% increase),*
- *3 missing PPAFs would result in 5 additional non-compliant cases per month (~38% increase),*
- *2 missing PPAFs would result in 14 additional non-compliant cases per month (~107% increase), and*
- *1 missing PPAF would result in 42 additional non-compliant cases per month (~323% increase)."*

In addition, the TRIG states that they considered: *"…the establishment of more strict corrective action guidelines (as proposed in the 16OCT2017 response to FDA), which will result in a higher volume of prescriber suspensions and deactivations* [discussed in comment "c" directly below]. *Therefore, the TRIG proposes that the increase in noncompliant cases by 38% balances the goals of making prescribers aware of the importance of compliance and patient safety without impacting patient access."*

The TRIG's arguments are about the additional work that will be placed upon them in notifying prescribers about their non-compliance as well as the fact that the implementation of criteria that will ban a prescriber for non-compliance will affect patient access. **Given the concerns that the FDA has regarding the high use of TIRFs in opioid non-tolerant patients (See Section 5.5.2. of this review) as well as continued concerns with the TIRF adverse event data as compared to other opioids (See Section 5.5.4 of this review) the FDA believes that the number of PPAFs associated with a non-compliance event should be one.**

b. In the 48 month RAAL, the FDA noted that the TRIG reported the number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. The FDA stated to the TRIG that "It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of timely completion of PPAFs." In the current report, the TRIG states that they *"…will further query noncompliant prescribers to determine more specific reasons of*

why they were not compliant with the REMS requirements. The TRIG will assess these responses to determine appropriate actions."
The FDA looks forward to reviewing the findings of the TRIG's query and assessment of responses in their subsequent assessment reports.

c. The Assessment report continues to include cases of prescribers who receive numerous Notices of Violation, Warning Letters, and then file several CAPs before one is accepted. Yet, these prescribers are not suspended or deactivated from the program. As noted to the TRIG in the 48-month RAAL, it is unclear what types of non-compliance actions would reliably lead to prescriber suspension or deactivation. In the 48-month RAAL, the TRIG was asked to add increased specificity to their Non-Compliance Review Team (NCRT) protocol as well as to the Supporting Document of the REMS. In the current Assessment Report, the TRIG states only that they *"…will consider updates to the Non-Compliance Protocol and the Supporting Document to add increased specificity around how non-compliance actions may lead to suspension or deactivation.*"

At the October 2, 2017 telecon between the FDA and the TRIG, the TRIG was once again urged to develop clear and specific criteria to their NCRT non-compliance protocol. In the TRIG's October 16, 2017, response, the TRIG presented the following criteria: "*The Corrective Action Guidelines within the Non-compliance Protocol will be modified to remove the second level of Notices, Warnings and Suspensions, thereby reducing the number of non-compliant events that can occur prior to deactivation of a non-compliant stakeholder, including prescribers. Once non-compliance has been confirmed, the revised non-compliant event schedule will include the following actions.*

- *A first offense of non-compliance will result in a Notice*
- *A second offense of non-compliance will result in a Warning*
- *A third offense of non-compliance will result in a Suspension*
- *A fourth offense of non-compliance will result in a Deactivation*

As a result of both changes, a stakeholder, including prescribers, will be deactivated from the program upon four non-compliant events."

After deliberating internally, the FDA review team decided that the TRIG should lower these 4 stages into 3 stages, and that the TRIG should eliminate their first (Notice) stage. Thus the first non-compliance event would be a Warning, the second event would results in a Suspension, and the 3rd even would result in a deactivation for a 3-year period.

d. In the 48-month RAAL, the FDA expressed concern that all three instances where a non-closed system pharmacy dispensed a TIRF product after a REMS rejection were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The FDA then suggested that the "*TRIG should develop a more active mechanism by which to identify and prevent such occurrences*". In the current assessment report the TRIG states that they are "…*looking into a more active mechanism to identify and prevent instances where a non-closed system pharmacy dispenses a TIRF product after a TIRF REMS rejection is received*." In addition, in response to an April 28, 2017 IR to the TRIG, the TRIG verified that they have "…*no way to systematically and accurately track if a pharmacy receives this rejection and still makes the decision to dispense*" and that "*All of these referenced instances would only be captured through spontaneous reports to the TIRF REMS Access program*."

   It seems likely that relying solely on spontaneous pharmacy self-reports of non-compliance will lead to an overall under-reporting in pharmacy non-compliance with the REMS. The TRIG needs to develop concrete and more active processes to address this deficiency in their compliance program and implement these processes expeditiously.

e. In the 36-month RAAL, FDA pointed out the poor results of both governmental entities (Veteran's Health Administration [VA] and Department of Defense [DoD]) closed-system pharmacies. The RAAL requested that the TRIG "*Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report*." In the 48-month Assessment Report the TRIG responded that "…*the current prescription authorization volume for closed system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time*." Thus in the 48-month RAAL, the FDA communicated to the TRIG that "*If the TRIG does not favor a novel authorization process for all of the closed-system pharmacies solely due to the poor performance of the governmental entities, the TRIG should propose an outreach to these programs to improve compliance*." In the current Assessment Report, the TRIG reiterates that the current prescription authorization volume for closed system pharmacies is <1% of all TIRF prescriptions and closed system pharmacies account for <1% of all pharmacies enrolled in the REMS. The TRIG also reiterates that no complaints have been received from closed system pharmacies regarding the authorization process. In addition, the TRIG states that challenges to updating the REMS authorization process to include a

web-based modality include: the transient nature of pharmacy staff at these locations; the need for staff re-education if such a modality is implemented; and the fact that some closed pharmacy locations are unable to access the internet.

In the Agency's April 28, 2017 IR to the TRIG, the Agency asked the TRIG to provide their sources of information for the challenges listed by the TRIG since the Agency believes that some of these obstacles cited would also apply to other closed and non-closed systems. In the TRIG's May 30, 2017 response, they state that these reasons are "anecdotal information" and that they do "*…not believe that these obstacles noted apply to other non-closed systems, as by definition a non-closed system pharmacy under the REMS is able to support the process of electronically transmitting validation and claim information*."

Given the small volume of prescriptions coming from closed systems as well as the overall good level of compliance with non-switch processes (by the non-governmental systems), the FDA agrees that a switch system should not be pursued. However, as stated in the 48-month RAAL, TRIG should insist that alternative approaches be taken by the two governmental entities. Examples of such alternatives could include: 1) both entities build in system alerts reminding pharmacists of the REMS requirements; and or 2) request that the two governmental entities develop a process requiring a two-person check when any TIRF is dispensed to ensure that REMS processes were followed. Likely there are additional processes that can be implemented. These alerts/revised processes should be in place and reported on starting with the December 2018 assessment report. In addition, the TRIG will be asked to provide an update is the February 28th assessment report submission regarding the TRIG's consideration of a quarterly evaluation of closed system pharmacy data,

f. In the 48-month assessment report, 6 inpatient pharmacies either did not respond to the audit request or decided not to participate. In the current assessment report, 3 of 12 pharmacies (25%) did not respond to an audit request and the TRIG states that they are "*…considering revisions to this (pharmacy) enrollment form to allow for process audits so as to increase the potential pool of inpatient pharmacies in the audit and will communicate any required modifications during the review of the next REMS assessment*." The FDA agrees that the TRIG should consider this revision and looks forward to learning of the TRIG's decision regarding this enrollment form.

5. As the TRIG has stated in previous reports, they state in the current assessment report that there were no reports of TIRFs being prescribed to an opioid non-tolerant individual or cases of inappropriate conversions between TIRF products. The Agency has previously commented that spontaneous reports are not suitable to assess the extent of TIRF use in opioid non-tolerant patient or the extent inappropriate interchanges between TIRF products. Opioid Tolerance analyses performed by the TRIG previously are discussed in this review's section 5.5.1.1., and the individual TRIG Sponsors submitted opioid tolerance data for their applications on June 15, 2017 which remain under review by the review team.

5.5. ASSESSMENT ELEMENT 5: SAFETY SURVEILLANCE

The fifth element of the Assessment Plan states:

Safety Surveillance (data collected per reporting period):

- *a. TIRF TRIGs will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the TRIG's respective Standard Operating Procedures*
- *b. TIRF TRIGs will produce one comprehensive report that presents spontaneous adverse event data from all TRIGs of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:*
  - *i. Line listings under each category of adverse events of interest as listed above*
  - *ii. Line listings should provide at a minimum the following information (see sample table provided):*
    1. *Identifying case number*
    2. *Age and Gender of the patient*
    3. *Date of the event as well as of the report*
    4. *The Preferred Terms*
    5. *Indication of TIRF use*
    6. *Duration of TIRF therapy*
    7. *Concomitant medications*
    8. *Event Outcome*
  - *iii. Other metrics of interest include:*
    1. *Number of event reports in each event category of interest*
    2. *Counts of adverse events related to inappropriate conversions between TIRF products*

3. *Counts of adverse events related to accidental and unintentional exposures*
4. *Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients*

iv. *Duplicate cases are identified and eliminated*

v. *Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such*

vi. *For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year*

c. *Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:*

vii. *Non-medical use of prescription drugs*

viii. *Surveys conducted at substance abuse treatment programs*

ix. *College surveys*

x. *Poison control center data*

xi. *Impaired health care workers*

xii. *Drug-related hospital emergency department visits*

xiii. *Drug-related deaths*

xiv. *Other databases as relevant*

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

5.5.1. Review of the TIRF REMS 48-Month Supplemental Report

5.5.1.1. Opioid Tolerance

DRISK previously reviewed the opioid tolerance data in the TIRF REMS 48-Month Supplemental Assessment Report[4]; however, given both the import and complexity of these data, DRISK consulted with our colleagues in the Division of Epidemiology II (DEPI) for a review of the data in the 48-Month Supplemental Assessment Report to review: 1) TRIG's drug utilization protocol and report regarding the TIRF REMS goal of "prescribing and dispensing TIRF products only to appropriate patients, which includes use only in **opioid-tolerant** patients[5], and 2) TRIG's persistency analysis protocol and report regarding the TIRF REMS goal of "preventing inappropriate conversion between TIRF products." DEPI was asked to assess the suitability and appropriateness of each protocol, as well as the two data reports regarding their methods, database choices, and data analyses, in accomplishing two of the objectives of the REMS goal and provided a review[6] with their findings to DRISK.

In the Supplemental Report, the TRIG used the IMS Health Longitudinal Prescription Database (LRx) to capture opioid dispensations prior to a TIRF product dispensation to estimate **opioid tolerance**. In the outpatient retail pharmacy setting, approximately 63% of patients dispensed a TIRF had a new or refill opioid analgesic prescription dispensed in the 8-30 days prior to being dispensed a TIRF. DEPI believes that looking at opioid prescriptions 8-30 days prior to a TIRF prescription may be a reasonable proxy to evaluate opioid tolerant status. However, DEPI expressed concerns with the use of only the LRx database:

> "*The LRx database appears to be an appropriate database for assessing U.S. outpatient retail TIRF utilization patterns, as the majority of TIRF products were sold from manufacturers to outpatient retail pharmacies. However, drug utilization data from other settings of care, such as inpatient settings and clinics, are not available. Calculating daily dose and length of therapy, especially for PRN products, based on days' supply and product strength may not accurately reflect what is being taken by the patient, particularly for opioid products that induce drug tolerance.* ***Specific data on directions for use (signa) are needed to establish daily dose estimates for opioids, yet this information is not included in the database used.*** *Days' supply of a dispensed prescription is estimated by the pharmacist, and the minimum and maximum daily dose that the patient may take depends on*

[4] May 4, 2016 REMS Supplemental Assessment Submission from the TRIG

[5] See also section 5.5.2 for product-specific analyses of opioid tolerance

[6] May 2, 2017 DEPI II (D.T. Coyle and T. Pham) Review of 48-Month TIRF REMS Assessment Data

his/her level of pain during the day. DEPI feels strongly that opioid tolerance status cannot be inferred from utilization or claims data; as such, all analyses employing this metric in these data sources must be interpreted in the context of this significant limitation."

With regards to the finding that 63% of patients dispensed a TIRF had a new or refill opioid analgesic prescription dispensed in the 8-30 days prior to being dispensed a TIRF, DEPI also cites concerns whether this finding necessarily indicates that these patients met the definition of opioid tolerance:

"The above data only show the percentage of patients who received an outpatient opioid analgesic prescription in the 30 days prior to the initial TIRF product prescription. These patients might not meet the definition of being opioid-tolerant as defined in TIRF product labeling, as daily opioid doses may vary depending on individual factors. As mentioned previously, DEPI feels strongly that daily opioid dose cannot be accurately inferred from utilization or claims data due to the phenomenon of tolerance, so using daily opioid dose as a surrogate for opioid tolerance status in this analysis is inadequate."

In addition, DEPI had concerns with the TRIG's use of a 1-7 day pre-TIRF prescription look-back period:

" The 1-7 day pre-TIRF opioid fill metric is problematic because a patient may not be capable of being opioid-tolerant as defined by the label, as they may have only been taking an opioid for <7 days before receiving the TIRF. Stratifying by new or refill prescription status within this timeframe would be useful: a patient receiving a new opioid analgesic prescription 3 days before an index TIRF prescription is incapable of being opioid-tolerant as defined by the label. However, a patient receiving a refill opioid analgesic prescription 3 days before an index TIRF prescription has the potential to be opioid-tolerant."

The TRIG performed a sensitivity analysis which excluded individuals with no claims for any product prior to receiving a TIRF product – roughly simulating a baseline enrollment history requirement. This analysis increased the estimates of patients who received a new or refill opioid prescription 8-30 days before TIRF receipt to approximately 75%. DEPI expressed concerns with this analysis:

"The original analysis did not restrict inclusion based on a pre-determined period of insurance coverage (and therefore data capture), so the sensitivity analysis is meant to exclude "new"-looking users from the pharmacies in their catchment area who look like non opioid-tolerant patients, but who may or may not have had pre-existing opioid prescriptions that were not seen with their data stream…This sensitivity analysis was not pre-specified, but rather was "implemented in the course of assessing data quality." While its results are somewhat more reassuring than those in the main analysis, it

is not clear how valid this sensitivity analysis is given our knowledge of the data source and its limitations."

Lastly, DEPI had concerns about the exclusion of pediatric patients from these analyses:

"Pediatric patients were excluded from the analysis, but the analysis does not specify the count of these excluded patients. Accidental ingestion and inappropriate use of fentanyl products among pediatric populations is a serious public health concern. Use of TIRF products in these excluded populations may represent inappropriate prescribing, and the Agency will need additional detail on the frequency with which this occurred."

5.5.1.2. Persistency Analysis

The TRIG's pharmacy switch database was the data source for the persistency analysis and uses outpatient TIRF prescription data collected from March 12, 2012 to October 28, 2015.

The results indicate that the persistency with index regimen was 45.2% at 6 months and 30.2% at 12 months for the total cohort. Overall, 20.5% of 18,160 patients changed their index TIRF regimen, and 25.6% of those patients had a change in their second TIRF regimen. Approximately 10% of patients remained on their index or second TIRF regimen, 65-70% of patients discontinued their TIRF regimen completely, and 27 patients filled at least one prescription for all five TIRF products available during the study period.

DEPI had the following concerns with how these data were calculated and presented:

"The above numbers and calculations are confusing and unclear. If a patient is on a second TIRF regimen, that implies he/she switched from a first TIRF regimen. However, this does not appear to have been accounted for in a clear manner, as the numbers do not add up correctly. Further, if 20.5% of patients changed their index TIRF regimen, that implies that 79.5% did not switch their index TIRF regimen. However, the final sentence indicates that 65-70% of patients changed their TIRF regimen by discontinuing their TIRF regimen. These metrics' lack of clarity, and the apparently-overlapping definitions employed regarding switches vs. discontinuations vs. changes, render this analysis very difficult to interpret."

"The persistency analysis and its results are very difficult to interpret. The definitions employed appear overlap [sic] with each other, and the metrics switch between describing the index, secondary, and other TIRF regimens throughout. It is not always clear to which denominator (index, secondary,

etc.) the various percentages refer. It is unclear how the various numbers relate to each other, or what the numbers mean."

In addition, DEPI had concerns about the data source used as well as some of the assumptions made in the conduct of this study:

"It is unclear why the persistency analysis excluded patients with only one prescription dispensed. These people only "persisted" through one prescription, and by excluding them, the analysis overestimates persistency. While it would be appropriate to exclude these individuals from a switching analysis, it is inappropriate to exclude them from a persistency analysis."

"By requiring follow up time in the database after cohort entry, the analysis captures only survivors and will exclude individuals who die after taking fentanyl – either from the condition the drug is treating, or from the drug itself. This approach conditions on the future, and is inappropriate because it introduces survivor bias."

DEPI also notes:

"*However, this analysis is most flawed in that the data source is unable to inform dose accurately due to its lack of prescriber instructions. Dose is the primary consideration for the REMS assessment of inappropriate switching…without dose data, it is not possible to determine whether a conversion between TIRF products was appropriate or inappropriate."*

The overall conclusions reached by DEPI regarding both studies are as follows:

"*All of these studies used data sources with insufficient detail to adequately inform their analyses…Future analyses of these questions should use a data source that contains prescriber instructions to address these concerns. A chart review within an integrated healthcare system – one that captures patient encounters across inpatient and outpatient settings, as well as prescription drug data with prescriber instructions to determine dose – may provide sufficient granularity to inform the question of interest. Using data from a single integrated healthcare system may decrease external validity because patients who opt into a given integrated program may not be representative of all TIRF product users. As such, it may be necessary to use data from multiple integrated systems to enhance the generalizability of the results."*

Comments to the Sponsor are included in Review **Section 9.**

5.5.1.3. Reviewer Comments

1. After further discussions with DEPI, it was decided that for the time being we would defer asking for the signa (instructions for use) data because: 1) few databases contain these data and 2) instructions for use for "as needed"

(prn) prescriptions often contain a huge range of possible daily doses, and thus may not provide the specificity needed.

5.5.2. Product-Specific Assessment of Opioid Tolerance

5.5.2.1. Introduction

In the November 10, 2016 REMS Assessment Acknowledgement Letter, the TRIG was told that: "The first objective (prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients) is not being achieved. In the TRIG's assessment of opioid tolerance, approximately 42% of patients prescribed TIRF products were not opioid-tolerant. It is important that the TRIG further investigate this issue." Thus, after a March 3, 2017 telecon between the FDA and the TRIG, the TRIG agreed on March 10, 2017 that each NDA/ANDA member of the TRIG would submit analyses of their product's use in opioid-tolerant/non-tolerant patients.

5.5.2.2. Overview of the Studies

Analysis #1: TIRF REMS Access Program Assessment: NDA/ANDA-Specific Utilization of TIRF Products in Opioid Non-Tolerant Patients (First Class-Wide Fill)

In Analysis 1, the IMS Longitudinal Prescription database (LRx) was used to identify patients who filled an initial outpatient prescription for a TIRF product (a **first class-wide fill**; all TIRF products included). The same data extract that was used in the original 48-Month TIRF REMS Supplemental Assessment Report was used in Analysis 1." Results were based on the first class-wide fill and then stratified by individual TIRF product. Product-specific results were then reported for the subset of patients whose initial outpatient class-wide fill was for each product of interest.

Analysis #2: NDA/ANDA-Specific Utilization of TIRF Products in Opioid Non-Tolerant Patients—First Product Fill (First Individual Product Fill)

In Analysis 2, in contrast to Analysis 1, the initial prescription fill was the first outpatient fill for a **specific TIRF Product (STP)**. This analysis was the "***first individual product fill approach***" (irrespective of prior fills for other TIRF products). In Analysis 2, the results were calculated based on the initial fill for each individual product of interest and reported separately for each product. To accurately identify prior opioid analgesic prescriptions, a new analytic dataset was compiled. This provided the opportunity to review and update National Drug Code (NDC) codes that were part of the REMS during the study period. Product-specific results were then reported for all patients with an initial outpatient fill for the product of interest.

In both Analysis 1 and 2, previous outpatient opioid prescription fills were assessed from February 11, 2012 to October 28, 2015 (the study period). Data collected were used to identify the proportion of patients who received an opioid analgesic product, including those concordant with the TIRF REMS definition of opioid tolerance.

5.5.2.3. Objectives

The objectives for the studies were to determine, for each individual TIRF product:

- By year, the number of total unique patients dispensed an initial prescription for a specific TIRF product in the outpatient setting.
- What proportion of those total unique patients received a prescription for an opioid analgesic product prior to the initial prescription for a specific TIRF product**.**
- Provide data separately for patients receiving an opioid analgesic within the 7 days prior and within the 30 days prior to the initial specific TIRF product prescription.

5.5.2.4. Primary Outcomes

The primary outcomes for Analysis 1 (first class-wide fill) and Analysis 2 (first individual product fill) were to:

1. Estimate the total number of unique patients dispensed an initial prescription for a TIRF product in the outpatient setting by year.
2. Estimate the proportion of unique patients who received a prescription for an opioid analgesic product within the 7 days prior to the prescription for the TIRF product (with TIRF fill on Day 0) and had days' supply of therapy consistent with the TIRF REMS definition of opioid tolerance.
3. Estimate the proportion of unique patients who received a prescription for an opioid analgesic product within the 8-30 days prior to the prescription for the TIRF product and had days' supply of therapy consistent with the TIRF REMS definition of opioid tolerance within the 30 days prior.

5.5.2.5. Study Data Source

This study used data from the LRx database, which contains electronic dispensed records of prescription claims at the anonymized patient level collected from US retail, specialty, mail order, and long term care (LTC) pharmacies (outpatient only; prescription medications delivered during inpatient stays are not available). The database represents dispensed prescriptions for **86% of the retail pharmacy channel, 40-75% of specialty and mail-order prescriptions (depending on therapeutic area), and about 50% of LTC (across therapeutic areas).** Data are available from 2003 and approximately 95% of claims are available for analyses within 12 days of being dispensed.

The database includes de-identified patient-level longitudinal data such as age, sex, 3-digit ZIP codes, **dispensed drug (through National Drug Code (NDC),** molecule, form**, strength, quantity, and days supply**. The database flags whether a prescription fill is a **first fill or refill**. Other relevant data include physician specialty, method of payment, and patient out-of-pocket costs. The database contains data for over 220 million unique de-identified patients and one million physicians.

All of the individual reports were prepared by QuintilesIMS.

5.5.2.6. Inclusion and Exclusion Criteria

The study **inclusion criteria** for Analysis 1 (first class-wide fill) were:

- Patients with ≥1 initial prescription fill for a TIRF product (class-wide) from an outpatient pharmacy, including retail and traditional mail order;
- For individual product subanalyses: patients whose initial outpatient class-wide prescription fill was for a STP

The study **inclusion criteria** for Analysis 2 (first individual product fill) were:

- Patients with ≥1 initial prescription fill for a STP from an outpatient pharmacy, including retail and traditional mail order.

The study **exclusion criteria** for both Analysis 1 and 2 were:

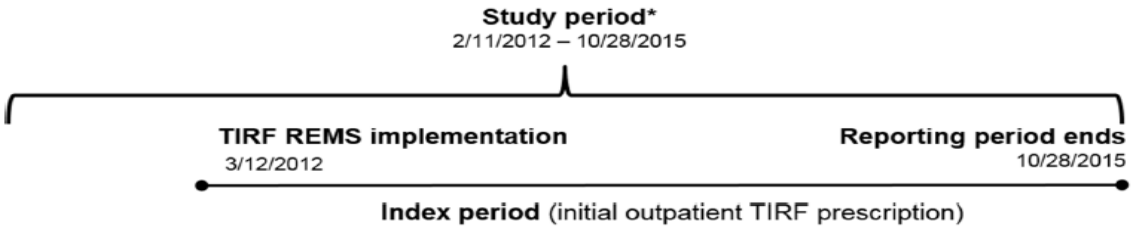
- Patients with age inconsistent with TIRF product labeling: younger than 16 years of age for Actiq and oral transmucosal fentanyl citrate lozenge generics; younger than 18 years of age for other products.
- TIRF product prescription fills from a long-term care pharmacy.

5.5.2.7. Study Periods

The study period was February 11, 2012 through October 28, 2015. The index period for both Analysis 1 (first class-wide fill) and Analysis 2 (first individual product fill) was March 12, 2012 (when the TIRF REMS began) through October 28, 2015.

In Analysis 1 (first class-wide fill), an initial class-wide TIRF prescription was defined as the first outpatient prescription fill for a TIRF product during the index period (see **Figure 2**, copied from the submitted reports). First prescription fill was identified based on the new fill/refill flag indicating the fill was new. Pre-index period exposure to TIRF products was not assessed because this study focused on initial TIRF prescriptions once the TIRF REMS Access program had begun. Specific TIRF products are included in Analysis 1 individual product analyses.

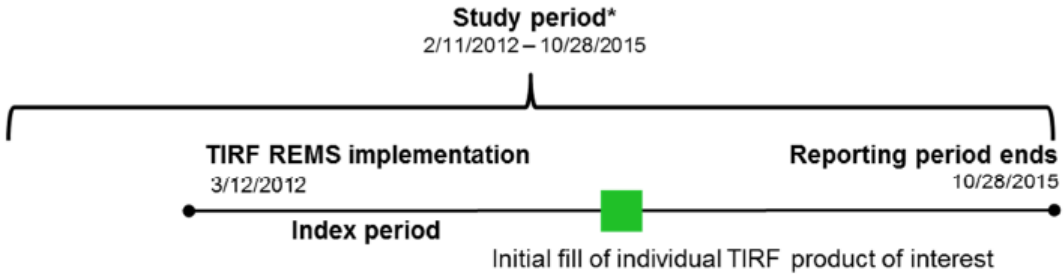
Figure 2: Study period and index period for Analysis 1 (first class-wide fill)



*Study period began 2/11/2012 to accommodate the ascertainment of opioid analgesic product prescriptions 30 days prior to each initial TIRF prescription.

In Analysis 2 (first individual product fill), initial individual product fill for a STP was defined as the first outpatient prescription fill for a STP during the index period. First prescription fill was identified based on the new fill/refill flag indicating the fill was new. As with Analysis 1, pre-index period exposure to TIRF products was not assessed. Analysis 2, provided the opportunity to review and update the NDC codes and as a result, the number of patients with an initial outpatient class-wide fill for any TIRF product may differ in the Analysis 1 and Analysis 2 datasets. (See **Figure 3**, copied from the submitted reports).

Figure 3: Study period and index period for Analysis 2 (first individual product fill)



*Study period begins 2/11/2012 to accommodate the ascertainment of opioid analgesic product prescriptions 30 days prior to each initial TIRF prescription.

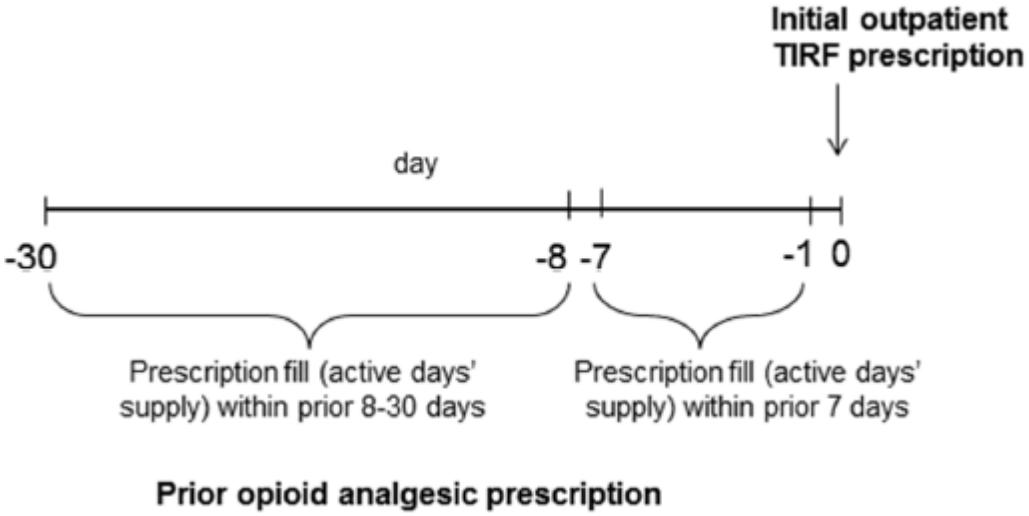
5.5.2.8. Prior prescriptions of opioid analgesic products

Prior prescriptions of opioid analgesic products were identified as ≥1 outpatient prescription fill for opioid analgesics dispensed within 30 days prior to the initial prescription fill for a STP (not including the date of this initial fill). This approach was the same for Analysis 1 (first class-wide fill) and Analysis 2 (first individual product fill). As a change from the TRIG's prior criteria to define opioid tolerance, prior prescriptions are restricted to patients with prescription fill dates within 30

days prior to the index date and do **not** include active supply extending from a prescription filled more than 30 days before the index date.

Opioid analgesic product prescription within 8-30 days prior to the initial TIRF (depicted as Day 0 in **Figure 4,** copied from the submitted reports) as assessed as was opioid analgesic product prescription within 7 days prior to the initial TIRF prescription fill.

Figure 4: Prior opioid analgesic use ascertainment period



5.5.2.9. Opioid Tolerance & Calculation

Opioid tolerance was assessed in the same way for Analysis 1 and Analysis 2. Per the TIRF REMS, patients are considered opioid tolerant if, for one week or longer, they took at least:

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/hour
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day

—OR—

- An equianalgesic dose of another oral opioid.

Daily dose was calculated for each prescription fill as follows:

a. Products/routes specifically listed in the REMS (e.g., oral morphine):

$$\frac{\text{Units dispensed} \times \text{Strength per unit}}{\text{Days' supply}}$$

b. Equianalgesic dose of another oral opioid:

$$\frac{\text{Units dispensed} \times \text{Strength per unit} \times \text{Conversion factor}^{1}}{\text{Days' supply}}$$

1 The source of the conversion factors is: Centers for Medicare & Medicaid Services (CMS). Opioid conversion factors, March 2015. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf

The TRIG notes that the TIRF REMS-specified cutoffs equate to different morphine equivalence values. For example, the cutoff for hydromorphone is 8 mg/day, which— applying the conversion factor of 4—is equivalent to 32 mg/day of oral morphine. This is lower than the REMS-specified cutoff of 60 mg oral morphine/day, which can make specific equianalgesic dosing imprecise, especially for combination products.

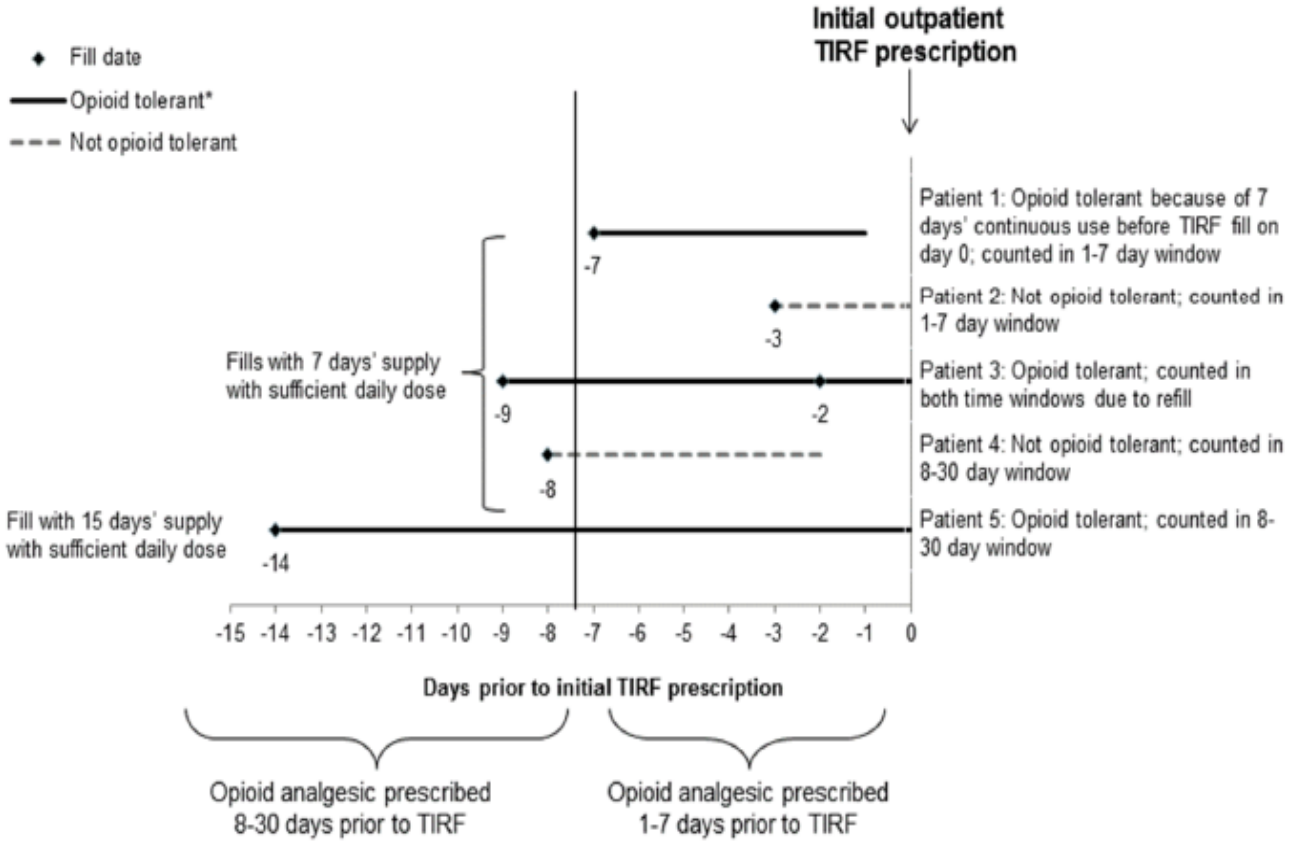
Patients met the criteria for **opioid tolerance** if they had **at least 7 continuous days of sufficient daily dose immediately preceding the date of the initial** TIRF prescription fill. A 1 day grace period between prescription fills was permitted to define serial prescriptions.

Patients who received an opioid analgesic product prescription within 7 days prior to the initial TIRF prescription fill were only considered opioid-tolerant if the opioid prescription fill was a refill or if it was new but filled 7 days prior to the initial TIRF prescription fill.

Patients with opioid analgesic product prescription fills that occurred more than 30 days prior to the initial TIRF prescription fill were still considered opioid-tolerant if all other criteria were met. For example, a patient with a 45-day continuous supply of sufficient daily dose filled 40 days before the index date would be considered opioid-tolerant. However, this patient would not be counted as having received a prior prescription of an opioid analgesic product dispensed within 30 days.

Figure 5 (copied from the submitted reports) illustrates how 5 patients would be classified as opioid-tolerant or opioid non-tolerant. Because of refills and concurrent use of multiple opioid analgesic products, a patient may be counted in both the 7-day and 8 to 30-day prior opioid analgesic prescription groups (as illustrated by example Patient 3 in Figure 5 below).

Figure 5: Examples of opioid tolerance classification for patients with opioid analgesic prescription fills prior to initial Fentora prescription fill



*Patients were considered opioid tolerant if they had ≥1 prescription fill with at least 7 continuous days of an opioid analgesic product and dose consistent with the TIRF REMS Access Program definition of opioid tolerance immediately preceding the TIRF prescription date.

5.5.2.10. Independent Variables and Other Covariates

The following demographic characteristics were collected:

- Age
- Sex
- Geographical region

5.5.2.11. Statistical Analysis

Descriptive statistics using frequency and percentage distributions were applied.
All analyses used SAS (SAS Institute Inc., Cary, NC).

5.5.2.12. Limitations

The TRIG's reports all stated the following limitations:

- Medication use estimated from claims data are still just estimates. The exact timing and quantity of use depends on actual patient behavior and can only be estimated. In particular, prescription days supply values may lead to overestimation of opioid tolerance because estimates are for maximum use possible based on the instructions for use, but the patient may in actuality use them less often for immediate-release products are dosed "as needed."
- Lack of hospital data in the LRx means that inpatient opioid analgesic use is not captured, which could result in underestimation of opioid tolerance for recently hospitalized patients.
- Concurrent use of multiple opioid products cannot be distinguished from product switching in the LRx. This may lead to overestimation of opioid tolerance in cases where a patient was down-titrated

5.5.2.13. Results

Analysis 1 Results

A total of (b) (4) unique patients who received initial outpatient TIRF prescriptions between March 12, 2012 and October 28, 2015 were identified in the LRx database. LRx quality control procedures resulted in the removal of 1,815 patients (6.6%). Thus a total of (b) (4) unique patients who met Analysis 1 study inclusion and exclusion criteria received an initial outpatient prescription for a TIRF product (any class-wide product) between March 12, 2012 and October 28, 2015.

Table 15 presents the demographics of patients for the 7 individual TIRF products that submitted reports as well as for TIRFs as a class:

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(b) (4)

5.5.2.14. Review of Older Opioid Tolerance Data

At an August 9, 2017, internal meeting between DRISK, DEPI, and DAAAP to discuss the above opioid tolerance data, Sharon Hertz, M.D., the Director of DAAAP recalled data submitted previously by two TIRF Sponsors that indicated a much higher level of opioid tolerance in patients initiating TIRFs. Dr. Hertz recalled:

- The April 15, **2008** submission[7], from the Sponsor (at that time) of **Fentora**, stated that (b) (4) of patients took at least the opioid dose required for opioid tolerance 90 days prior to Fentora
- Similarly, the August 17, 2001 Periodic Safety Update Report (PSUR)[8], from the Sponsor (at that time) of **Actiq**, stated noted that (b) (4)

On August 10, 2017, FDA sent an Information Request (IR) to the Sponsor of **Fentora** and received a response on August 24, 2017. In that response, the Sponsor stated that:

- The current Sponsor, Teva, bought the product from Cephalon and "*…most personnel who worked on the 2008 report are no longer employed by Teva*." As such, the current Sponsor stated that they were not able to locate the original protocol for their data.
- The Sponsor also stated that they were *"…unable to confirm that this means that the patient had a prescription for the around-the-clock medication sometime in the 90-day period and prior to the Fentora prescription…"…without any time frame defined to indicate that the around-the-clock prescription durations were directly adjacent to or overlapping with the initial Fentora prescription…it is possible that the around-the-clock opioid was stopped sometime prior to the initiation of Fentora*."
- The Sponsor also stated that the same patient may have been counted in more than one quarter as a new patient and that this could mask a decline in opioid tolerance
- The Sponsor concluded that the "*2017 analysis is considered a much tighter time frame between the around-the-clock opioid prescription and the first Fentora prescription*."

Similarly, on August 16, 2017, FDA sent an Information Request (IR) to the Sponsor of **Actiq** and received a response on August 30, 2017. In that response, the Sponsor again noted that:

- The current Sponsor, Teva, bought the product from Cephalon and "*…most personnel who worked on the 2008 report are no longer employed by Teva*." As such, the current Sponsor stated that they were not able to locate the original protocol for their data.

[7] April 15, 2008 RiskMap 5th Quarterly Report, supporting Document #94

[8] August 17, 2001 Periodic Safety Update Report (PSUR)-16, Supporting Document #102

- What the Sponsor was able to gather is that this information about opioid tolerance was gathered as a result of a patient survey. Patients who received Actiq were recruited from 4 participating pharmacy chains and received follow-up calls from the Sponsor in which:
    - Patients were provided with reminders about safe use; and
    - Patients were asked: ***Was the patient already on a strong opioid when they received the ACTIQ prescription?***
- The Sponsor stated that they have no information about the numbers of patients surveyed
- The Sponsor also offered that the question asked of patients assumed that patients understood not only what a "strong opioid" is but that patients were not confusing it with a different pain medication. Thus there is no way to determine whether the use of this "strong opioid" met the requirements for opioid tolerance (dose/duration) prior to Actiq.
- The Sponsor concludes that these data are *"…likely to have been much less accurate than the recent 2017 estimation…."*

5.5.2.15. Reviewer Comments

1. The TIRF Sponsors have provided two separate analyses, a First Class-Wide Fill analysis (Analysis 1) and a First Individual Product Fill analysis (Analysis 2), each with sensitivity sub-analyses. Sensitivity subanalyses were performed on the subset of patients who had at least one outpatient fill for any product in the 30 days prior to the initial TIRF product prescription fill with the objective of trying to minimize misclassifying patients as not opioid-tolerant simply because the LRx database did not contain any data about them previously.

   The reported proportions of opioid non-tolerance in patients receiving TIRFs were lower in Analysis 2 than in Analysis 1. Sensitivity sub-analyses further lowered percentages obtained from either analysis. However, regardless of the analysis, the proportion of opioid-non-tolerant patients receiving a TIRF product ranged from a low of 34.6% up to 55.4%. Thus the proportion of patients receiving TIRFs as calculated by these analyses remains concerning.

   However, there are limitations of the TRIG Sponsor's analyses as follows:
    a. Estimating opioid tolerance from outpatient claims data has a number of potential pitfalls:
        i. Claims data do not typically contain instructions for use
        ii. Prescription days' supply calculations (especially for prn or "as needed" instructions) may overestimate opioid tolerance since calculations of daily dose typically look at the maximum daily dosage possible (based on the instructions for use), but

in actuality the patient may use the product much less often than the instructed daily maximum dosage.

iii. Since inpatient opioid analgesic use is not captured, opioid tolerance may be underestimated especially for recently hospitalized patients.

iv. Concurrent use of multiple opioid products cannot be distinguished from product switching, potentially leading to an overestimation of opioid tolerance in cases where a patient was down-titrated

b. It is not clear to this reviewer which analysis submitted by the TRIG Sponsors is the most appropriate - First Class-Wide Fill analysis or a First Individual Product Fill. In any future submissions of such data, if the TRIG would choose to provide a similar analysis, the TRIG should include only data regarding the first class-wide fill (as opposed to the first individual product fill). The first class-wide fill likely indicates the patient's first exposure to a TIRF, and thus these are the patients we are most concerned about should they not be opioid-tolerant at the time of initiating a TIRF.

c. The data submitted by the TRIG Sponsors are in a format that does not permit a year by year analysis of opioid tolerance. Thus it is not possible to determine whether the use of TIRFs in opioid non-tolerant patients is increasing or decreasing. In any future submissions of such data, the TRIG should provide yearly calculations of opioid tolerance to allow for this evaluation.

2. The Sponsors' inclusion of Figure 5 providing examples of under what circumstances a patient would or would not be considered opioid tolerant is reassuring in that the criteria applied to determine opioid tolerance look to be very logical.

3. Overall the submitted opioid tolerance data do not reveal much difference in the use of any particular TIRF product versus another TIRF product in opioid non-tolerant patients. A visual inspection of the data reveals that *perhaps* Abstral is very slightly less likely than other TIRFs to be used in opioid non-tolerant patients.

4. With regard to the older data on use of either Actiq or Fentora in opioid on-tolerant data, despite the limitations expressed above with the 2017 analysis, this current analysis is much more reliable than the older opioid tolerance data previously reported by the Sponsor of both products.

5. The submitted data indicate that the typical TIRF patient is female, is between 35 to 64 years of age, and resides in the South.

6. Lastly, in the TRIG's October 16, 2017, response to the October 2, 2017, telecon between the FDA and the TRIG, the TRIG notes that: "*Based on an analysis previously conducted by Insys, the proportion of patients who were opioid-tolerant was substantially higher (77%). Therefore, the TRIG will further investigate the difference between the algorithm used in the TRIG analyses and that used by Insys before proceeding with the validation study. The TRIG has investigated several data options for the validation study and has narrowed the selection to the below two choices* [The Henry Ford Health System (HFHS) and Optum's Clinformatics Claims Data and Integrated Claims-EMR Data]. *Further discussions with each of these data source companies are ongoing, and TRIG will notify the FDA which option was selected following resolution of the above referenced algorithm comparison*." DEPI reviewed the proposed data sources for the opioid tolerance algorithm validation and provided some feedback about which data source would be better suited for the validation and the information that should be included with a protocol submitted by February 2, 2018. DEPI expressed concern about any further delay in the validation efforts and suggested that the TRIG validate both algorithms, if necessary, to prevent delay. The TRIG was also asked to design an assessment of adverse events among patients using TIRFs who were not opioid-tolerant. Discussions of this study continued in their October 16, 2017 responses to the October 2, 2017 teleconference, and DEPI provided more guidance on appropriate data sources for the study that are described in the RAAL.

5.5.3. Pharmacovigilance Review

5.5.3.1. Introduction

To better inform whether or not one of the TIRF objectives – "*Preventing accidental exposure to children and others for whom it was not prescribed*" was being met, and the extent of off-label use of TIRF products, as well as whether any reports of use of TIRF products in opioid non-tolerant patients have been received, DRISK consulted the Division of Pharmacovigilance II (DPV) on March 10, 2017 to conduct an analysis of cases contained within the FDA Adverse Event Reports System (FAERS cases). DPV provided their review[9] on July 20, 2017 and their findings will be summarized here.

- [9] July 20, 2017 Pharmacovigilance review (C. Patel) regarding TIRF accidental exposures and off label use

5.5.3.2. Methods

DPV evaluated cases of accidental exposure and off label use with a TIRF product. The following definitions were applied:

- **Accidental exposures -** unintended exposure to a TIRF product temporally associated with an adverse event (HLT: Accidental exposures to product)
- **Off label use -** Cases reporting use of a TIRF product for an unlabeled indication or in an unlabeled population temporally associated with an adverse event (HLT: Off label uses)

US cases from **November 4, 1998 – May 9, 2017** were examined and DPV used the FBIS Quick Query.

The review points out that FAERS data have limitations:

- No certainty that the reported event was actually due to the product.
- FDA does not receive reports for every adverse event or medication error that occurs. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event in the U.S. population.

5.5.3.3. Accidental Exposures Results

A total of 237 cases were identified. Of these cases:

- 80% of cases were in patients <1 to 6 years of age
- The TIRF products involved were as follows:
    - 190 – Actiq
    - 16 – Fentora
    - 10- Subsys
- The following serious outcomes were reported:
    - Hospitalization – 26
    - Death – 10
    - Life-threatening – 5
    - Other serious - 56

DPV then reviewed a randomly selected 25% (n=59) of the reports from the accidental exposure FAERS search and after applying certain case definitions, 19 cases were included in the in-depth look at adverse events associated with accidental exposure to a TIRF. Cases of accidental exposure to a TIRF were most frequently reported in children, including 14 cases in children 5 years of age or younger. All 14 cases reported exposure to Actiq, the majority of the events occurred in 2010 or earlier.

5.5.3.4. Off-Label & Opioid Tolerance Results

A total of 740 cases of off-label use were identified. Of these cases:

- In 53% of cases, the age was unknown; in 38% the age was between 17-65 years of age
- The TIRF Products involved were:
  - 248 (34%) – Actiq
  - 202 (27%) – Fentora
  - 107 (14%) – Subsys
- The following serious outcomes were reported:
  - Death - 89
  - Hospitalization - 116
  - Life-threatening – 6
  - Other serious – 185

DPV manually reviewed a randomly selected 25% (n=185) of the TIRF reports retrieved from the two off-label use FAERS searches. Approximately 30% (19/66) of the cases included a serious outcome, including nine cases of hospitalization and/or death. There were two cases with an outcome of death.

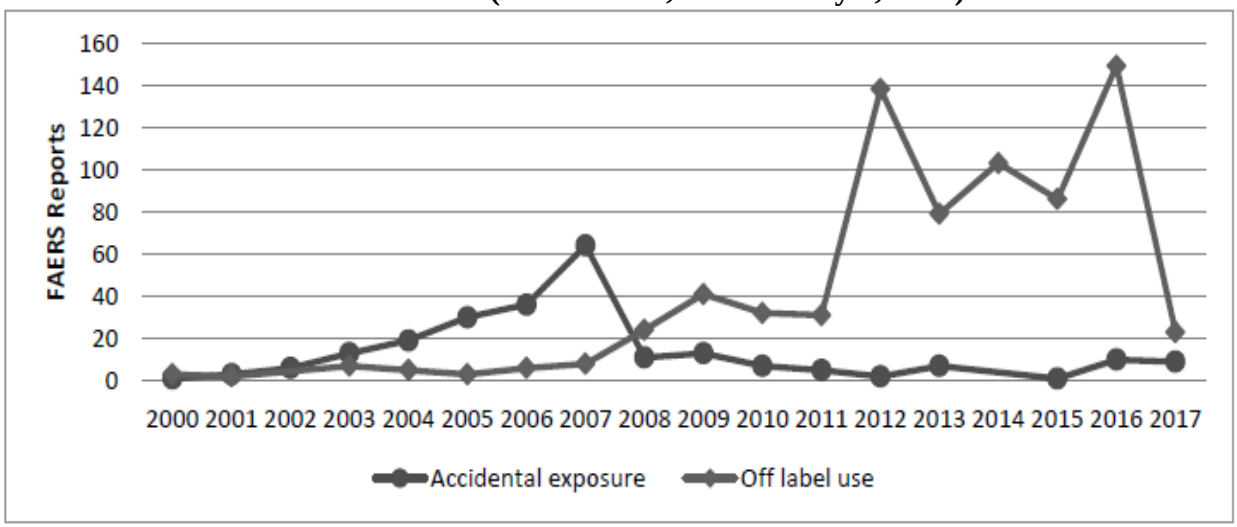
When indication was reported, TIRF products were most frequently used for pain, back pain, migraine, and headaches.

Thirty-six cases of off-label use reported concomitant around-the clock (ATC) opioid treatment or self-reported tolerance to opioids. Of the 36 cases, 15 were opioid-tolerant, 20 were not assessable (provided the ATC medication and, in some instances, the dosing frequency but did not report the dose), and one was opioid non-tolerant (did not meet the ATC dosing outlined in the labeling) although the opioid non-tolerance did not play a contributory role in the adverse event associated with the off-label use of the TIRF product.

The review did not identify any cases of off-label use in opioid-naïve patients nor did DPV identify any cases with sufficient detail to assess appropriateness of TIRF product conversion.

Figure 6 (taken from the DPV review's Figure 1) presents the number of FAERS reports gathered yearly since 1998 for both accidental exposure and off-label use:

Figure 6. Accidental Exposure and Off Label Use FAERS Reports (N=977)* by Initial FDA Received Year (November 4, 1998 to May 9, 2017)



* These reports may include duplicates or reports not meeting the case definition criteria.

Especially since 2011, the numbers of reports of off-label use of TIRFs have greatly increased.

5.5.3.5. Reviewer Comments

1. FAERS reports of off-label use greatly exceeded reports of accidental exposures. Also, there was a sudden increase in reports of off-label TIRF use starting after 2011. Whether the fact that the REMS was launched on December 2011 has had any impact on these reports is unknown.

2. Regarding accidental exposure reports, 80% of cases were in patients <1 to 6 years of age, with Actiq being the TIRF product most often mentioned in these reports.

3. Regarding off-label use reports, in 53% of these cases, the age of the patient was unknown whereas in 38% the age was between 17-65 years of age. Actiq remained the TIRF product most frequently cited.

4. Of the currently marketed TIRF products, Actiq is the oldest, having been approved in November 1998; therefore, the fact that this is the TIRF product most often mentioned in the reported cases is likely at least partly related to its time on the market.

5. The most common off-label uses of TIRF products were for pain, back pain, migraine, and headaches.

6. There was only one report of a TIRF used in an opioid non-tolerant patient. Reviews of previous assessments have discussed the limitations of searching for incidents of opioid non-tolerance in FAERS reports.

7. It should be noted that the DPV review did not look to capture opioid non-tolerant events used when TIRF are used in cancer patients.

5.5.4. Review of TIRF REMS 60-Month Surveillance Data

DRISK also consulted DEPI to provide an assessment of the utility and appropriateness of the provided surveillance data in determining whether the goals of the REMS are being met. Additionally, DRISK asked DEPI to comment on whether the data were useful for continued surveillance purposes and to recommend any additional data sources that may be useful in assessing whether the REMS is meeting its goals.

See DEPI's review[10] for description of RADARS programs/data sources and outcome definitions. As per agreement with FDA, the safety surveillance analyses requested by FDA necessitated slightly different time periods as noted in the relevant sections within the report.

Table 27 below (reproduced from Table 2 of DEPI's review) summarizes the basic study design characteristics of the surveillance data (consisting of spontaneous adverse event reports and RADARS data):

Table 27: Surveillance Study Design Characteristics

Study Design Characteristic	Details for This Study
Time Period	60- month report observation periods
Spontaneous adverse event reports	8/29/2015-8/28/2016

- [10] August 4, 2017 DEPI II (T. Meyer) Review of 60-Month Transmucosal Immediate-Release Fentanyl (TIRF) Product REMS Assessment Data

RADARS® surveillance data	
Pre-REMS period	7/1/2010-6/30/2012
Post-REMS period	7/1/2012-6/30/2016
Study design	Ecologic
Exposure	All TIRFs on the market during the study period combined into one category
Comparators	**Primary comparators:** 1. **Schedule II immediate release opioids** (oxycodone, non-transmucosal fentanyl, hydromorphone, morphine, oxymorphone, tapentadol) 2. **Schedule II opioids** (oxycodone, non-transmucosal fentanyl, hydromorphone, morphine, oxymorphone, methadone, tapentadol) 3. **Schedule II opioids excluding methadone** (oxycodone, non-transmucosal fentanyl, hydromorphone, morphine, oxymorphone, tapentadol) Since hydrocodone was not a schedule II opioid for the entire study period, it was excluded from the primary analysis and then included as a schedule II drug for the entire study period as a secondary analysis.
Outcomes	1. Inappropriate conversion 2. Unintentional therapeutic exposures 3. Unintentional general exposures 4. Non-opioid tolerant use 5. Addiction 6. Intentional misuse 7. Abuse 8. Overdose 9. ED visits/hospitalizations 10. Pediatric exposures 11. Death 12. Major medical outcomes and death

Denominators	• **Number of population** extrapolated from 2000 and 2010 US Census per quarter • **Number of retail prescriptions** from IMS Government Solutions, Inc. projected to national level retail prescriptions per quarter • **Number of dosage units** from IMS Government Solutions, Inc. projected to national level retail dosage units per quarter
Analysis	• Quarterly AE rates were calculated by dividing the number of events from various RADARS data sources by the sum of population, prescriptions, or dosage units for the 3-digit zip code covered by the program from US Census or IMS Health data. • Poisson regression was used to compare changes in the rates of outcomes before and after the REMS was implemented. Both a comparison of means and a comparison of trends were evaluated. For the comparison of means, the mean quarterly rates of outcomes were calculated for the pre- and post-periods and the differences in means were compared across time periods. For the comparison of trends, trend lines were fit to the pre- and post-periods and slopes were compared between the periods. The report claimed that the comparisons of means provided a better fit to the data but did not provide any statistics or explanation to support that assertion.

Appendix Section 10.3. summarizes the characteristics of the spontaneous adverse events data and RADARS data used in this submission.

RESULTS:

A detailed description of the results is included in **Appendix Section 10.4.**

Spontaneous Adverse Event Data:

Table 28 below (taken from the DEPI review's Table 5) compares the adverse event rates across the three most recent reporting periods for addiction, death, overdose, and pediatric exposures:

Table 28: Adverse Event Rates during the 36, 48, and 60-month Reporting Periods[a,b]

	60-month reporting period 8/29/2015-8/28/2016			48-month reporting period 8/29/2014-8/28/2015			36-month reporting period 8/29/2013-8/28/2014		
AE of interest	N	Rate per 100,00 Rx (N= (b) (4)	Rate per 100,000 Patients (N= (b) (4)	N	Rate per 100,00 Rx (N= (b) (4)	Rate per 100,000 Patients (N= (b) (4)	N	Rate per 100,00 Rx (b) (4)	Rate per 100,000 Patients (N= (b) (4)
Addiction	6	(b) (4)		12	(b) (4)		5	(b) (4)	
Death	344			294			400		
Overdose	4			6			2		
Pediatric exposure	3			4			2		

AE, adverse events; Rx, prescriptions

a Rates are the counts of the specific adverse event from divided by 1) the population size from US Census data, 2) the number of prescription fills from IMS Health data, or 3) the number of dosage units from IMS Health data.

b Reviewer-generated table based on information presented in Tables 28 and 29 of the 60-month REMS assessment report

DEPI reports that of the 344 deaths this reporting period, causality for 200 deaths could not be determined; 121 were determined to be unrelated to the TIRF; 4 deaths were possibly related to TIRFs and 1 death was due to the inappropriate use of a TIRF. All three pediatric events were from the intentional use of TIRFs; the outcomes from 2 cases were unknown while the third case had outcome of 'not recovered/resolved'.

RADARS Data:

DEPI states that these data include:

- cumulative case counts (each person counts once per outcome) and case mentions (multiple mentions are possible per person per outcome)
- quarterly rates per 100,000 population, 10,000 prescriptions, or 100,000 dosage units from the pre- to post-REMS periods,
- percent change in the slope (95% CI) of the trend line for the quarterly abuse rates from the pre- to post-REMS periods.

TRIG states that the percent mean difference in quarterly rates in the pre- and post-REMS periods was a better fit to the data than the quarterly trend lines, although no data were included to substantiate this. DEPI focused mostly on the percent mean difference, but also provided the percent difference in slope in the tables.

DEPI also states that they focused on the prescription-based rates since the population-based rates were very low as compared to the comparator products (e.g., immediate-release [IR] opioids), given the large differences in utilization. DEPI further explains that they focused upon the prescription-adjusted rates rather than the dosage unit-adjusted rates since TIRF product dosage forms such as nasal or sublingual sprays can potentially differ from transmucosal lozenges in how these dosage forms are counted. For example, DEPI points out that there are eight sprays/dosage units per bottle of Lazanda, and pharmacies may record a quantity of one for the bottle or a quantity of eight to reflect the actual number of dosage units.

Table 29 (a modification of DEPI's Table 6) presents the percent changes in adverse event rates for TIRFs versus comparator opioids from the pre- to post-REMS periods for the Poison Center and other RADARS programs:

Table 29: Percent change in adverse event rates for TIRFs and comparator opioids outcome between the pre- (7/2010-6/2012) and post-REMS (7/2012-6/2016) periods in the Poison Center Program and Other RADARS Program data

	Outcome		Cumulative Cases	% change in **means** (95% CI) per 10,000 prescriptions	% change in **slope of trend lines** (95% CI) per 10,000 prescriptions
Poison Center Program	Abuse	TIRFs		(b) (4)	
		C2 IR opioids			
	Intentional Misuse	TIRFs			
		C2 IR opioids			
	Unintentional Therapeutic Error	TIRFs			
		C2 IR opioids			
	Unitentional General Exposure	TIRFs			
		C2 IR opioids			
	Emergency Department Visits and Hospitalization	TIRFs			
		C2 IR opioids			
	Major Medical Outcome and Death	TIRFs			
		C2 IR opioids			
Treatment Center Program	Abuse Rate	TIRFs			
		C2 IR opioids			
College Survey	Non-Medical Use	TIRFs			
		C2 IR opioids			
IHCW	Abuse Rate	TIRFs			
		C2 IR opioids			

With regards to the Poison Center data, DEPI notes the very small numbers of events throughout which likely causes the large variability in the results. Regarding the specific studied outcomes, DEPI notes the following:

- (b) (4)

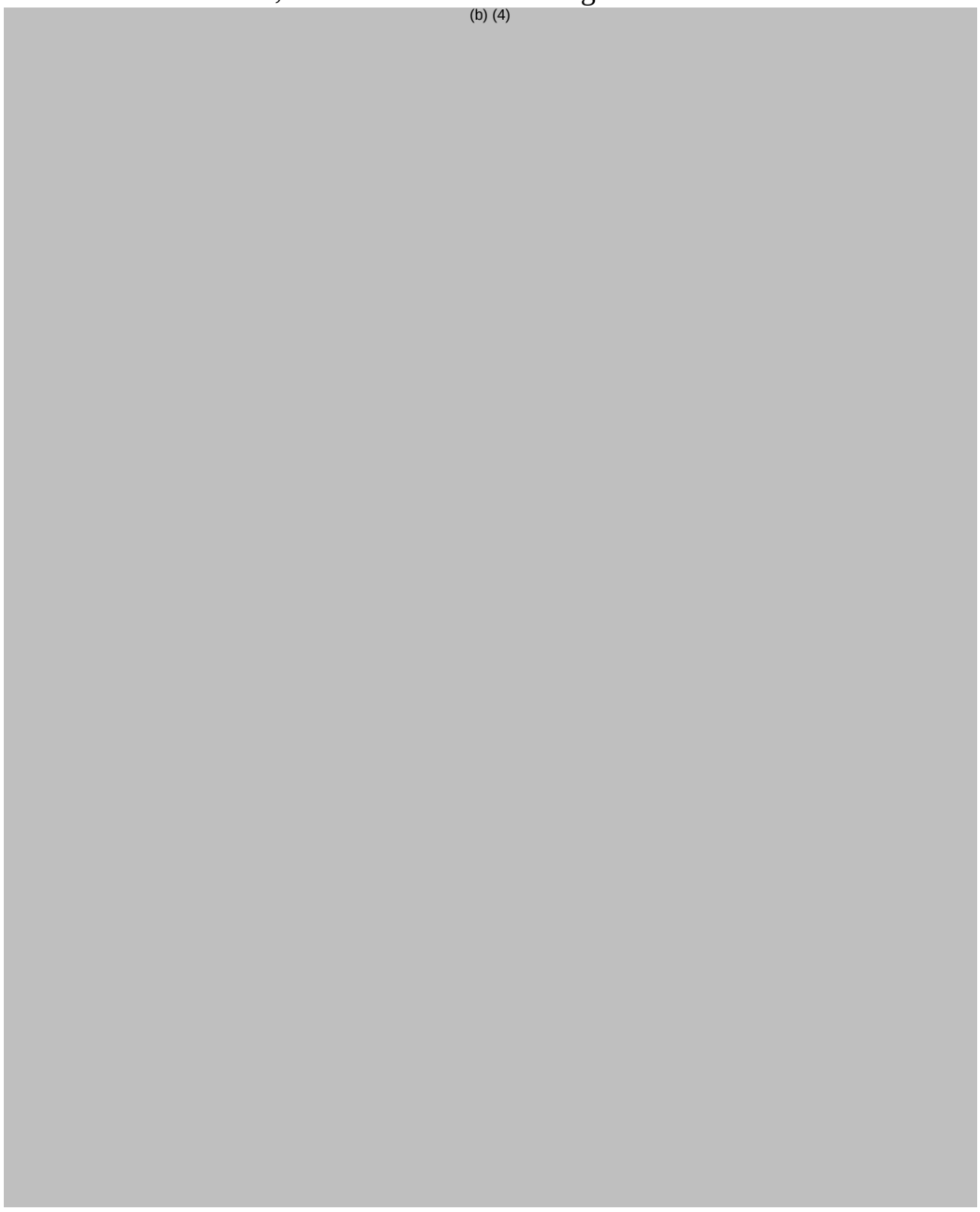


Figure 7 (taken from the TRIG report's Figure 8.1.1.3) compares RADARS intentional abuse mentions per 10,000 prescriptions dispensed via a comparison of means from July 2010 through June 2016 for TIRFs and comparator products:

Figure 7: RADARS Poison Center Program Intentional Abuse Exposure Mentions per 10,000 Prescriptions Dispensed Comparison of Means from July 2010 through June 2016 for TIRFs and Comparators

(b) (4)

Figure 8 (taken from the TRIG report's Figure 8.1.7.3) compares RADARS Treatment Center Programs combined last month use to get high mentions per 10,000 prescriptions dispensed via a comparison of means from July 2010 through June 2016 for TIRFs and comparator products:

Figure 8: RADARS Treatment Center Programs Combined Last Month Use to Get High Mentions per 10,000 Prescriptions Dispensed Comparison of Means from July 2010 through June 2016 for TIRFs and Comparators

(b) (4)

Figure 9 (taken from the TRIG report's Figure 8.1.8.3) compares RADARS College Survey Program past 3 month nonmedical use mentions per 10,000

prescriptions dispensed via a comparison of means from July 2010 through June 2016 for TIRFs and comparator products:

Figure 9: RADARS College Survey Program Past 3 Month Nonmedical Use Mentions per 10,000 Prescriptions Dispensed Comparison of Means from July 2010 through June 2016 for TIRFs and comparator products

TIRF Products Schedule II IR Opioids

(b) (4)

DEPI's Summary of Findings:

- "*The data suggest that the* ***prescription-adjusted rates for past 30-day abuse or past 90-day non-medical use of TIRFs have increased over time*** *even as the utilization of TIRFs has decreased as a group.*
- *The* ***abuse and non-medical use rates increased most notably after the REMS was established*** *which roughly coincides with the approval of Subsys. Product-specific results are needed to ascertain if certain TIRF products are driving the increase.*
- *The data suggest that the* ***rates of abuse and non-medical use, after adjusting for the number of prescriptions dispensed, are substantially higher for TIRFs than for the existing composite comparator groupings.***
- *Although based on small numbers of cases, there appeared to be an* ***increase in the rate for unintentional therapeutic errors; emergency department visits and hospitalizations; and major medical outcomes/deaths for TIRFs*** *from the pre- to post-REMS periods, when adjusted for prescriptions dispensed, whereas the comparator rates decreased.*"

DEPI states their concern with the above findings given that trends for most comparators were decreasing over time. DEPI emphasizes that analysis by product is needed to determine whether or not these increases are a class effect or limited to specific products. Limitations in the data that they cite are:

- "*small event counts for TIRF exposure, especially in PCP data*
- *representativeness of the treatment center sources*
- *misclassification of specific TIRF or comparator exposures*
- *limited capture of outcomes of interest in the Poison Center data, and*
- *voluntary reporting of exposures and outcomes across the data sources which may introduce misclassification bias*."

DEPI's Overall Conclusions/Recommendations:

"***We cannot assess whether the REMS was effective in mitigating the outcomes of interest with the current presentation of the data. However, these data may be useful for assessing the REMS effectiveness with respect to the overarching goals of reducing abuse, misuse, and unintentional exposures given the modifications described here. The number [sic] events may be too small, after stratifying by product, to be useful for assessing the REMS, especially for some of the Poison Center Program analyses.*** *Although we cannot determine from the current presentation of data whether the REMS had a mitigating effect on these trends, the current presentation of the data suggests that, despite the presence of a REMS,* ***we observed an increasing trend in prescription-adjusted rates of abuse and other significant outcomes for TIRFs over the time period***."

DEPI had the following specific observations:

1. *"…Currently, the Sponsors have provided data for all TIRFs, combined, and for large groups of composite comparators. Grouping multiple drugs may mask variability and trends for individual drugs…Therefore, further submissions should separate the TIRFs by product, where possible under the confines of a shared system REMS. Generics and branded products that are the same dosage forms may be combined. In addition, composite comparator groups of multiple products and molecules should not be used. Instead, we recommend oxycodone IR, oxycodone ER, hydromorphone IR, and oxymorphone IR as comparators. Please note that one document showing trends for individual TIRF products will be significantly easier to evaluate for REMS effectiveness and for surveillance purposes than having each product submitted in separate reports.*

2. *…To assess the effectiveness of the REMS, we have to examine patterns in AE rates before and after the REMS for the products that had no REMS implemented prior to the shared system REMS. Reporting results by TIRF product will address this need.*

3. *The P-values provided are not very meaningful given the large number of tests performed and the small number of events attributed to TIRFs…With the small numbers of events it may not be possible to power the assessments appropriately, especially since we want to assess product-specific outcome rates that will split the small numbers of cases further. We will likely have to base our assessments on the descriptive data reporting the magnitude of changes in AE rates over time for TIRF and comparator products. The Sponsors should interpret the magnitude of changes instead of or in addition to statistical significance. Statistical significance of results should only be incorporated into the interpretations when sufficient a priori power was present.*

4. *Report case and mention counts for both the pre- and post-REMS periods.*

5. *Limit the TCP data to the centers that participate in the TCP for the majority of the study period as a sensitivity analysis to improve the ability to trend numbers over time.*

6. *Consider reporting the Poison Center results as annual rates rather than quarterly rates to help stabilize the variability due to small numbers of events.*

7. *Provide separate results for children under 6 years of age in the unintentional exposure AE results.*

8. *Remove the Impaired Healthcare Worker data as they add little value to our understanding of the trends in outcomes of interest related to these products*."

DEPI also offered the following suggestions to the TRIG for "streamlining the presentation of surveillance data:

- *"The Sponsors need to clarify their finding that the comparison of means rather than the comparison of slopes is the best fit for the data. If we agree with their assessment, dropping the tables and figures with comparisons of slopes and intercepts will also help streamline these assessments.*
- *DEPI can provide table shells to streamline the presentation of results further once we understand whether the slope and intercept data are essential.*

- *Visual inspection of the quarterly rates over time will still be useful for identifying possible trends.*"

Additionally, DEPI recommended that the TRIG use the following additional surveillance data sources to assess the following outcomes:

- Unintentional Pediatric Exposures: "*Additional data sources for identification of unintentional pediatric exposures were proposed in a separate review. Possible data sources suggested for exploration were 1) death certificate data where fentanyl form (i.e., TIRFs) may be reported in the literal text on the death certificates and 2) emergency department administrative claims data with linkages to electronic medical records. Accidental poisonings in children could be identified via ICD-10 diagnostic codes in claims data and the specific drug and drug form could be pulled from EMR records.*"

  [Note: DRISK consulted to DEPI as to whether the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) emergency department (ED) data could be a robust supplement to the TRIG's annual reports of accidental childhood exposures to TIRFs. DEPI concluded[11] that NEISS-CADES does not appear to be a robust source of cases of accidental pediatric exposures to TIRFs since there were only two TIRF-related accidental exposure ED visits reported from about 60 sampled US hospitals from 2004-2015 (the other 8 fentanyl exposures reported were attributed to the patch). The receipt of only two cases is well below the 20 needed to generate national estimates. DEPI's review also delves into reasons why cases were likely to be under-ascertained from NEISS-CADES. Thus, DEPI does not recommend adding NEISS-CADES ED cases as a routine surveillance source of accidental TIRF exposures in children.]

  FDA and the TRIG have had subsequent communications about these accidental poisoning analyses since DEPI finalized their review of the 60-month REMS Assessment Report; the most recent communication was a written response from the TRIG on October 16, 2017 which addressed discussion between the FDA and TRIG in an October 2, 2017 teleconference. Briefly, the TRIG agreed to conduct a study of ED visits and inpatient admissions to look for evidence of TIRF poisoning in provider notes within electronic medical records. They also agreed to evaluate various sources of death records for evidence of childhood deaths due to

[11] Meyer T, Kornegay C, and Staffa J. Epidemiology: Review of NEISS-CADES Data on Pediatric Emergency Department Visits Related to Accidental Exposure to Transmucosal Immediate Release Fentanyl. Filed 4/21/2017, Reference ID: 4084489

TIRF poisoning. DEPI provided responses to their October 16, 2017 communication that are included in section 9.

- Abuse: "*Further data are needed to describe abuse rates by drug in the general population. A new Survey of Non-Medical Use of Prescription Drugs Program under the RADARS system may be useful, but DEPI has not been able to fully evaluate the study methods yet. The survey began in the third quarter of 2016."*
- Overdose: "*Fatal overdoses may be identified in medical examiner data (by state, or possibly through requests for National Center for Health Statistics death certificate data analyses)."*

DEPI's Comments to the Sponsor are in **Review Section 9**.

5.6. ASSESSMENT ELEMENT 6: KNOWLEDGE, ATTITUDES, AND BEHAVIOR (KAB) SURVEYS

5.6.1. PATIENT SURVEY

The purpose of the patient survey was to assess patients' and caregivers' knowledge, attitudes, and behavior in terms of the safe use of TIRF medicines as described in the REMS educational materials. Patients/caregivers were eligible to participate if they were age 18 or older and had a prescription filled for a TIRF medicine within 120 days (4 months) prior to the survey launch date. Respondents were recruited through the TIRF REMS Access Program database and a Pharmacy Benefits Manager (PBM) via direct mail. The survey was conducted from September 26, 2016 to November 21, 2016. Survey invitations were sent to 2945 potential respondents with 399 returned as undeliverable. A total of 394 respondents accessed the survey, 374 answered at least one question, 321 were eligible, and 310 completed the survey. The survey closed early once 310 surveys were collected. The majority of respondents completed the survey via the internet (67%) followed by telephone (33%). According to patient reports, most respondents were between the ages of 50-69 (67%), female (64%), White (86%), and had some college/Associate's degree or higher (81%). The most commonly reported prescription was for Subsys (41%), followed by Actiq (23%), and Fentora (18%). Most respondents were from the South (35%), followed by the West (31%), Midwest (16%), and the Northeast (18%).

The TRIG compared survey respondents (n=310) with the general population of patients who have received a TIRF prescription in the last four months (obtained from IMS Health data) (n=3134). The populations were compared in the areas of TIRF products used, age, gender, race, ethnicity, geographic distribution, level of education, and main language spoken at home.

The Division of Biostatistics 7 (DB7) conducted a review of the comparison analysis to comment on the suitability/appropriateness of the comparison and the

conclusions of the sponsor and suggestions for improvement or changes. DB7 noted statistically significant differences between the two groups for "highest level of education completed" (p=<.0001) and "race" (p=<.0001). In terms of education, the level of education on average was higher for survey respondents than for the general population of TIRF patients. There were more survey respondents with some college versus the general patient population (44.5% versus 27%) and fewer survey respondents with high school (17% versus 31.5%) or less than high school diploma (2% versus 6%) than the general population. In terms of race, DB7 noted that there were more race categories in the survey than provided for the general population. For common race categories, there were fewer White survey respondents as compared to the general population (86% versus 89.5%), fewer Black or African American (4% versus 7%), and fewer Asian (<1% versus 1%). DB7 did comment that although race was significantly different between the two groups, in the most common categories, survey respondents and the general patient population had comparable proportions so this difference will not likely affect the correct response rate in the survey.

The survey contained questions about six key risk messages:

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 the 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.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.

This key risk message included questions about patients' and caregivers' knowledge of the life-threatening breathing problems that TIRF medicines can cause. The majority of respondents answered the question correctly for this key risk message (92%).

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.

This key risk message included questions about patients' and caregivers' knowledge that TIRF medicines should not be taken if they are opioid tolerant and understanding of what opioid tolerance is. The majority of respondents were aware

that opioid tolerance means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines (88%) and TIRF medicines should only be taken by patients that are opioid tolerant (89%). Overall, 83% of respondents answered both questions correctly for this key risk message and 12% answered 1 out of 2 correctly.

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

This key risk message included nine questions about patients' and caregivers' knowledge that TIRF medicines should be taken exactly as prescribed, the correct indication for TIRF medicines, knowledge that headache pain is not an appropriate indication for use of TIRF medicines, to stop taking TIRF medicines if they stop taking around-the clock opioid pain medicine, and it is not okay to take TIRF for short-term pain. All but one respondent were aware that TIRF medicines should be taken exactly as prescribed. The majority of respondents were aware that it is not okay to take TIRF medicine for short-term pain (85%) while fewer were aware that it is not okay to use TIRF medicines for headache pain (67%). Only 40% of respondents were aware that they should discontinue taking the TIRF medicine if they discontinue the around-the-clock opioid pain medicine. While most respondents were aware that TIRF medicine should not be used for headache pain (78%), dental pain (87%), respondents were unaware that TIRF medicines should not be used for long-lasting painful conditions not caused by cancer (39%) or pain after surgery (64%). In addition, only 73% of respondents reported the correct indication of breakthrough pain from cancer. Overall, 11% of respondents answered all nine questions correctly for this key risk message.

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

This key risk message included questions about patients' and caregivers' knowledge that they should not switch to another medicine that contains fentanyl without talking to a healthcare provider. The majority of respondents were aware that is not safe to switch to another medicine that contains fentanyl without discussing with a healthcare provider first (96%).

Key Risk Message 5: Patients should not give the TIRF medicines to anyone else even if they have the same symptoms.

This key risk message included questions about patients' and caregivers' knowledge that TIRF medicine should not be given away and selling or giving them away was against the law. The majority of respondents were aware that TIRF medicines should not be given to another person if they have the same symptoms as the patient (98%) and that selling or giving away TIRF medicines is against the law (99%). Respondents were also aware that a side effect of TIRF medicines is the chance of abuse or addiction (93%), TIRF medicines can be misused by people who abuse

prescription medicines or street drugs (97%), and that TIRF medicines should be kept in a safe places to prevent it from being stolen (99%). Overall, 88% of respondents answered all five questions correctly for this key risk message.

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.

This key risk message included questions about patients' and caregivers' knowledge that TIRF medicines should be stored in a safe place out of reach of children, disposed of as described in the specific product's Medication Guide (MG), can cause an overdose and death in any child who takes it, and what to do if an adult takes TIRF medicines that have not been prescribed. All respondents were aware that TIRF medicines should be stored in a safe place out of the reach of children. Most respondents were aware that TIRF medication must be disposed of as described in the specific product's MG (98%), that a TIRF medicine can cause an overdose and death in any child who takes it (94%), and if an adult who has not been prescribed a TIRF medicine takes it they should get emergency help right away (89%). Overall, 84% of respondents answered all four questions correctly for this key risk message.

Additional Safe Use Questions

The survey included five additional questions about the safe use of TIRF medicines and patient-reported prescriber behaviors related to use of TIRF medicines. Most respondents reported that their healthcare provider talked to them about the risks and possible side effects of TIRF medicines (86%), told them how to use the TIRF medicine (95%), and told them how to store or keep the TIRF medicine (87%). Knowledge scores have been consistent across the assessment periods. Most respondents were also aware that TIRF medicines are only available through a pharmacy enrolled in the TIRF REMS Access Program (77%).

Questions about REMS Educational Materials

The survey included questions about patients and caregivers awareness of the TIRF educational materials including the Medication Guide (MG) and the Patient-Prescriber Agreement Form. The majority of respondents reported ever receiving the Medication Guide (MG) (93%). Most respondents reported receiving it from the pharmacy (92%) each time a prescription was filled (91%). A little over half of respondents reported receiving the MG from their prescribing doctor or someone in the doctor’s office (57%), most at the first appointment (82%). The majority of respondents reported reading the MG (97%) with 92% reporting reading all or most of the MG. Most of the respondents (91%) reported understanding all or most of the MG. Most patients/caregivers reported that they did sign a Patient-Prescriber Agreement Form (77%) and received a copy of the form (77%). Respondents also

reported that their healthcare provider offered to explain the form (77%) and they understood all or most of the explanation (99%).

Summary of Findings

Overall, surveyed patients had a high level of knowledge (≥80%) across most of the key risk messages as in previous assessments, including awareness of the potential side effects of TIRF medicines (breathing problems, death), that TIRF medicines should be taken as prescribed, that TIRF medicines should only be taken by patients who are opioid tolerant, that you should talk to a healthcare provider before switching medicine, that selling or giving away TIRF medicines is illegal, and that TIRF medicines should be stored in a safe place.

Respondents were less aware of the correct indication for TIRF medicines with only 73% correctly selecting breakthrough pain from cancer. In addition, respondents were unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine with only 40% selecting the correct answer. Knowledge rates have consistently been low with these questions across assessment periods.

Most respondents reported receiving (93%) and reading (97%) the Medication Guide with 91% who reported receiving it from their pharmacy receiving it at every prescription fill. Seventy-seven percent (77%) of respondents reported signing the Patient-Prescriber Agreement Form and 77% of respondents were aware that TIRF medicines are only available through a special program, the TIRF REMS Access Program.

Reviewer's Comments

A. Respondents were unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine, with only 40% selecting the correct answer. Knowledge rates have consistently been low with these questions across assessment periods, and ways to improve knowledge in this area should be identified and implemented.

B. DB7: For the review of the comparison of the demographics of the patient survey respondents with the overall population of patients who are prescribed TIRF medicines, the survey respondents had a significantly higher "highest education level completed" than all users in the IMS database. Thus, we suspect the knowledge rate in the survey was overestimating the knowledge rate for all users. We request the following analyses from the sponsor.

    - Submit subgroup analyses stratified by education level, to quantify the impact of education on knowledge in the survey.

- Submit a sensitivity analysis predicting the knowledge rate in all users adjusting for education level in your survey (e.g. standardization)
- Submit the data for us to reproduce your results.

5.6.2. PHARMACIST SURVEY

The purpose of the pharmacist survey was to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines. Pharmacists were eligible to participate if they dispensed TIRF products in the past six months. Respondents were recruited from a random sample of pharmacists from pharmacies that were enrolled in the TIRF REMS Access Program as of September, 2016. Any pharmacist who worked at an enrolled pharmacy was eligible to participate. The survey was conducted from September 26, 2016 to December 13, 2016. Pharmacists were recruited via mail or fax. Three categories of pharmacies were sampled: Closed System Pharmacies (CSP), Inpatient Pharmacies, and Outpatient Pharmacies. Approximately 11,598 invitation letters were sent to pharmacists from 3856 enrolled pharmacies. From these, 561 pharmacists accessed the survey, 333 (59%) met the eligibility criteria, and 318 pharmacists completed the survey and completed the survey for a response rate of 3%. The majority of respondents completed the survey via the internet (99%) followed by telephone (1%). Approximately half of respondents were male (49%) and had been practicing pharmacy for 11 or more years (53%). Nineteen percent (19%) of respondents had never dispensed a TIRF medicine while 47% had dispensed a TIRF medicine one to two times per month. Actiq was most commonly dispensed (75%) followed by Fentora (41%), and Subsys (37%). Most respondents were from the South (40%), followed by the Northeast (24%), Midwest (20%), and the West (16%). The majority of respondents (75%) were not the pharmacist-in-charge. For the chain/independent pharmacies, there were 145 unique pharmacies with one completer; 40 with two completers, and nine with three completers. For the inpatient pharmacies, there were 29 unique pharmacies with one completer, 13 with two completers, and three with three completers. There was one participant from a closed system pharmacy.

The TRIG compared pharmacist survey respondents (n=240) with the general population of pharmacists that have dispensed a TIRF prescription in the last six months (REMS switch provider data) (n=3875) for region, type of pharmacy, and number of orders by type of pharmacy.

DB7 conducted a review of the comparison analysis to comment on the suitability/appropriateness of the comparison and the conclusions of the sponsor and suggestions for improvement or changes. DB7 noted statistically significant differences between the two groups for “type of pharmacy” (p=<.0001). In terms of

type of pharmacy, most of the survey respondents represented independent outpatient pharmacies (69%) while the general population of TIRF pharmacists was from chain outpatient pharmacies (34%).

The survey contained questions about five key risk messages: 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 or 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 to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients

This key risk message included questions about pharmacists' understanding of who is considered an opioid tolerant patient and that TIRF medicines are contraindicated in opioid non-tolerant patients because of the problems that can occur such as respiratory depression and death. Most respondents knew that cancer patients who are considered opioid tolerant are those who are taking around-the clock opioid therapy for underlying persistent cancer pain for one week or longer (96%) and that patients who have no known contraindications to fentanyl, but are not currently taking around the clock opioid therapy were not considered opioid tolerant (82%). Most respondents also knew that TIRF medicines can cause life-threatening respiratory depression or death if used in opioid non-tolerant patients (88%) and that all prescribers should begin with titration from the lowest dose available for all new patients even if the patient has taken another TIRF medicine before (84%). Overall, awareness was low in terms of the specific medication/dose that a patient would need to be taken for a patient to be opioid tolerant. While most respondents were aware that patients who are taking 60 mg oral morphine/day for one week or longer (88%) or 25 mcg transdermal fentanyl/hour (80%), were considered opioid-tolerant , respondents were less aware of the other regimens for opioid-tolerance (8 mg oral hydromorphone/day (75%), 30 mg oral oxycodone/day (78%), 25 mg oral oxymorphone/day (72%), and an equianalgesic dose of another oral opioid (65%)). Overall, 31% of respondents answered all thirteen questions correctly. Respondents who received and read the prescribing information or Medication Guide were more aware of the specific medication/dose for opioid tolerant patients than those that did not receive or read them.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age or older (16 years of age or older for Actiq) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

This key risk message included questions about pharmacists' knowledge of the correct indication for TIRF medicines and understanding of timing of administration of TIRF medicines. Most respondents were aware that breakthrough pain from cancer was the correct indication for TIRF medicines (92%). In addition, most respondents were aware of incorrect indications for TIRF medicines with the exception of only 51% aware that chronic non-cancer pain was not a correct indication. While 81% of respondents were aware that a cancer patient cannot start taking a TIRF medicine after one day on an around the clock opioid, only 62% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. Only 41% of respondents were aware that a patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine. Overall, 22% of respondents answered all eight questions correctly for this key risk message.

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.

This key risk message included questions about pharmacists' knowledge of the risk factors and signs and symptoms of opioid abuse in patient taking TIRF medicines. Almost all respondents were aware that a personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse was a risk factor for opioid abuse (99%) although only 77% were aware that a personal history of psychiatric illness was also a risk factor. Pharmacists were aware that it was important to monitor for signs of abuse and addiction in patients who take TIRF medicines (98%) and that TIRF medicines can be abused in a manner similar to other opioid agonists (94%). In addition, respondents were aware of the risks associated with TIRF medicines: misuse (99%), abuse (99%), addiction (99%), and overdose (99%). Overall, 59% of respondents answered all ten questions correctly for this key risk message.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

This key risk message included questions about pharmacists' knowledge that TIRF medicines are not interchangeable regardless of the route of administration. The majority of respondents were aware that TIRF medicines are not interchangeable (96%), that conversion of one TIRF medicine to another may result in a fatal overdose (93%), the dosing of TIRF medicines is not equivalent on a microgram-to-

microgram basis (89%), and TIRF medicines with the same route of administration cannot be substituted with each other if the pharmacy is out of stock for one product (96%). Overall, 80% of respondents answered all four questions for this key risk message. Respondents who received and read the prescribing information or Medication Guide were more aware that dosing of TIRF medicines is not equivalent on a microgram to microgram basis than those that did not receive or read them.

Average Knowledge Scores by Key Risk Message

Table 30 presents the average knowledge scores for each key risk message.

Table 30: Average Knowledge Score by Key Risk Message

Key Risk Message	Score [95% CI]
KRM 1	84% [82, 86]
KRM 2	75% [73, 78]
KRM 3	94% [93, 95]
KRM 4	94% [92, 95]
Overall	86% [84, 87]

Additional Safe Use Questions

The survey included additional questions about the safe use of TIRF medicines and pharmacist-reported activities performed related to use of TIRF medicines. Respondents were aware that TIRF medicines should not be sold, loaned, or transferred to another pharmacy (91%), that pharmacy staff must be educated about the TIRF REMS Access Program (90%), and that the use of TIRF medicines with a CYP3A4 inhibitor may require dosage adjustment and monitoring (92%). Most inpatient pharmacist respondents were aware that it is not ok to dispense TIRF medicines from the inpatient inventory to outpatients (83%) although the sample size was small (n=65).

In terms of pharmacist-reported activities, most respondents reported always performing the following activities or performing them only with the first prescription:

- Giving patients the MG for their TIRF medicine (87%; only with first prescription (8%)).
- Instructing patients not to share TIRF medicines (70%; only with first prescription (20%))

Responses were relatively low with respondents reported always performing the following activities or performing them only with the first prescription:

- Instructing patients on how to store or keep the TIRF medicines (62% only with first prescription (27%))
- Talk to patients about the risks and possible side effects of the TIRF medicines (48%; only with first prescription (39%))
- Asking patients about the presence of children in the home (55%; only with first prescription (27%))
- Instruct the patient on how to use the TIRF medicines (58%; only with first prescription (35%))
- Instructing patients about proper disposal of any unused or partially used TIRF medicines (62% only with first prescription (27%))
- Counseling patients that accidental exposure to TIRF medicines by a child may be fatal (65% only with first prescription (22%))
- Instructing patients to keep TIRF medicines out of reach of children (67%; only with first prescription (21%))

Only 40 (62%) of inpatient pharmacists reported having an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the REMS program. Most outpatient pharmacists (82%) reported processing all TIRF medicine prescriptions regardless of method of payment, through the pharmacy management system.

Questions about TIRF Medicine REMS Educational Materials

The survey included questions about pharmacists' access to educational materials for TIRF medicines. Almost all pharmacists reported receiving or having access to the Prescribing Information (96%), and the majority of those reported reading it (81%). Most respondents reported receiving or having access to the Medication Guide (MG) (97%) and 88% of those reported reading it. In addition, 87% of respondents reported always giving patients the Medication Guide.

Summary of Findings

Overall, surveyed pharmacists had a high level of knowledge (≥80%) across most of the key risk messages as in previous assessments, including awareness that TIRF medicines should only be given to opioid tolerant patients, that TIRF medicines have the potential to be abused and that TIRF medicines are not interchangeable with each other. While most respondents were aware of the correct indications for TIRF medicine, only 44% correctly stated that chronic non-cancer pain was not an approved indication. Only 75% of respondents were aware that a personal history of psychiatric illness was a risk factor for opioid abuse. Overall responses were low in terms of awareness of specific medication/dose for opioid tolerant patients with

the exception of oral morphine. Correct responses ranged from 65% to 89%. Almost all respondents reported having access to the Prescribing Information with 83% reading it. Similarly, all but one respondent reported having access to the Medication Guide with 88% reading it. While 92% of respondent reported always giving patients the MG for their TIRF medication, responses were low in terms of other behaviors including always: asking patients about the presence of children in the home (60%); counseling patients that accidental exposure to TIRF medicines by a child may be fatal (72%); and instructing patients about proper disposal of any unused or partially used TIRF medicines (69%). Only 62% of the inpatient pharmacy respondents reported having an established system, order sets, or protocols to ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program. The majority of outpatient pharmacies (82%) reported processing all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system.

Reviewer's Comments

A. There was only one closed system pharmacy (CSP) survey respondent. The TRIG should increase efforts to get participants from additional closed systems to participate in the survey.
B. Only 62% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. In addition, only 41% of respondents were aware that a patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine. Knowledge has consistently been low in this area across assessment periods, and ways to improve knowledge in this area should be identified and implemented.
C. Only 62% of the inpatient pharmacy respondents reported having an established system, order sets, or protocols to ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program. This should be explored further in program audits.
D. DB7: For the review of the comparison of the demographics of the pharmacist survey respondents with the overall population of pharmacists who prescribed TIRF medicines, the survey respondents differed from all pharmacists in the REMS switch provider data by type of pharmacies. This may bias the results but we do not know in which direction or by how much. We request the following analyses from the sponsor.
    - Submit subgroup analyses stratified by type of pharmacy, to quantify the impact of type of pharmacy on knowledge in the survey.
    - Submit a sensitivity analysis predicting the knowledge rate in all pharmacists adjusting for type of pharmacy in your survey (e.g. standardization)
    - Submit the data for us to reproduce your results.

5.6.3. PRESCRIBER SURVEY

The purpose of the prescriber survey was to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines. Prescribers were eligible to participate if they were enrolled in the TIRF REMS Access Program as of September 2, 2016 and had prescribed a TIRF medicine in the last six months. The survey was conducted from September 26, 2016 to December 20, 2016. Prescribers were recruited via mail. Approximately 2848 prescribers were invited to participate. A total of 8405 reminder letters were sent to non-responders. From these, 524 respondents agreed to participate and were screened and 313 prescribers were eligible with 294 completed the survey for a response rate of 10%. The majority of respondents completed the survey via the internet (98%) followed by telephone (2%). Most respondents were male (60%), were medical doctors (57%), and had been practicing medicine for 11 to more than 15 years (60%). Over half of the respondents have prescribed TIRF medicines about one to two times per month (64%) followed by 22% prescribing between three to more than five times per month. Five percent (5%) of respondents stated that they had not prescribed a TIRF medicine within the last six months. The main medical specialty was pain management (59%) followed by "Other" (16%), oncology (15%), and primary care (10%). Actiq or generic Actiq were most commonly prescribed (57%) followed by Subsys (54%), and Fentora (33%). Respondents represented all geographic regions with 32% from the West, 31% from the South, 21% from the Northeast, and 16% from the Midwest. Only 1% of respondents reported that they practiced in a closed healthcare system.

The TRIG compared prescriber survey respondent self-reported data (n=294) with prescriber survey respondent data from the REMS switch provider (n=294) and the general population of prescribers that had prescribed a TIRF medicine in the last six months (REMS switch provider (n=3045)) for average times per month TIRF medicines have been prescribed within the past six months, TIRF medicines prescribed within the last six months, and geographic region. A comparison was also completed between prescriber survey respondents (n=294) and prescribers of TIRF medicines in the past six months (IMS data) (n=(b) (4) on average times per month TIRF medicines have been prescribed within the past six months, TIRF medicines prescribed within the last six months, geographic region of practice location, gender, medical profession, number of years practicing medicine, and medical specialty.

DB7 conducted a review of the comparison analysis to comment on the suitability/appropriateness of the comparison and the conclusions of the sponsor and suggestions for improvement or changes. There were no significant differences between survey respondent's data and data provided from the REMS switch provider. There were statistically significant differences between the survey respondents and the general population of prescribers from IMS data for on average

times per month they prescribed TIRF medicines within the past six months (p=<.0001), TIRF medicines prescribed within the last six months, gender (p=0.0002), medical profession (p=<.0001), number of years practicing medicine (p=<.0001), and medical specialty (p=<.0001). Survey respondents were less likely to prescribe one to two times a month (64% versus 84%) and more likely to prescribe 3-5 times per month (22% versus 7%) as compared to prescribers from IMS data. Survey respondents were also less likely to be male (59.5% versus 71%), less likely to be MDs (57% versus 71%), more likely to have practiced medicine for a shorter timeframe (46% practiced for more than 15 years as compared to 61% IMS data), and more likely to have the specialty of pain management as compared to IMS data prescribers (37% versus 19%).

The survey contained questions about five key risk messages: 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 or 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 to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients

This key risk message included questions about prescribers' understanding of who is considered an opioid tolerant patient and that TIRF medicines are contraindicated in opioid non-tolerant patients because of the problems that can occur such as respiratory depression and death. The majority of respondents were aware that TIRF medicines should only be taken by patients who are opioid tolerant (97%). Most respondents knew that cancer patients who are considered opioid tolerant are those who are taking around-the clock opioid therapy for underlying persistent cancer pain for one week or longer (95%). The majority of respondents were also aware that patients were not opioid tolerant if they were not currently taking opioid therapy, but have taken opioid therapy before (94%) and if they have no known contraindications to the drug fentanyl, but are not currently taking around the clock opioids (93%). Most respondents also knew that TIRF medicines can cause life-threatening respiratory depression (92%) and death if used in opioid non-tolerant patients (96%). Respondents were also aware that TIRF medicines should not be used to treat opioid non-tolerant patients (88%) and that all prescribers should begin with titration from the lowest dose available for all new patients even if the patient has taken another TIRF medicine before (86%). Overall, respondents were aware of

the specific medication/dose for opioid tolerant patients: morphine (96%), 30 mg oral oxycodone/day (82%), 25 mg oral oxymorphone/day (80%) and transdermal fentanyl (89%). Respondents were less aware of the other regimens for opioid-tolerance (8 mg oral hydromorphone/day (72%), and an equianalgesic dose of another oral opioid (66%).Overall, 33% of respondents answered all fourteen questions correctly.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age or older (16 years of age or older for Actiq) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

This key risk message included questions about prescribers' knowledge of the correct indication for TIRF medicines and understanding of timing of administration of TIRF medicines. Most respondents were aware that breakthrough pain from cancer was the correct indication for TIRF medicines (99%) and stated that they inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraines, or any other short-term pain (96%). In addition, most respondents were aware of incorrect indications for TIRF medicines (acute or postoperative pain (95%); headache or migraine paint (94%); dental pain (96%)); with the exception of only 78% were aware that chronic non-cancer pain was not a correct indication. For respondents that indicated that chronic non-cancer pain was a correct indication, there was a follow-up question about what types of chronic pain conditions that they prescribed TIRF medicines for. Back pain was the top reported condition (17%), followed by chronic pain (15%), and cancer pain (11%). Respondents were also asked why a TIRF medicine was selected to treat these chronic pain conditions. The top responses were efficacy (24%), fast onset (11%), and other types of treatments have failed (11%). Only 72% of respondents were able to identify the patient that should not use a TIRF medicine based on the provided patient scenarios. In terms of awareness of the timing administration of TIRF medicines, 78% of respondents were aware that a cancer patient cannot start taking a TIRF medicine after one day on an around the clock opioid, 77% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time, and 77% of respondents were aware that it is incorrect to instruct patients to continue taking their TIRF medicine if they stop taking their around the clock opioid medicine. Overall, 33% of respondents answered all ten questions correctly for this key risk message.

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.

This key risk message included questions about prescribers' knowledge of the risk factors and signs and symptoms of opioid abuse and the importance of monitoring patients taking TIRF medicines. All respondents were aware that a personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse was a risk factor for opioid abuse (100%) while 86% were aware that a personal history of psychiatric illness was also a risk factor. Respondents were aware that it was important to monitor for signs of abuse and addiction in patients who take TIRF medicines (99%) and that TIRF medicines can be abused in a manner similar to other opioid agonists (96%). Respondents were aware that misuse (99%), abuse (99%), addiction (99%), and overdose (99%) were all risks associated with the use of TIRF medicines. Overall, 61% of respondents answered all ten questions correctly for this key risk message.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

This key risk message included questions about prescribers' knowledge that TIRF medicines are not interchangeable regardless of the route of administration. The majority of respondents were aware that TIRF medicines are not interchangeable (92%), that conversion of one TIRF medicine to another may result in a fatal overdose (96%), and the dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (92%). Only 79% of respondents selected the appropriate course of action in a proposed scenario converting a patient from one TIRF medicine to another. Overall, 70% of respondents answered all four questions for this key risk message.

Average Knowledge Scores for Each Key Risk Message

Table 31 presents the average knowledge score for each key risk message.

Table 31: Average Knowledge Scores for Each Key Risk Message

Key Risk Message	Knowledge Score [95% CI]
Key Risk Message 1	87% [86, 89]
Key Risk Message 2	86% [85, 88]
Key Risk Message 3	94% [93, 95]
Key Risk Message 4	90% [88, 92]
Overall Knowledge Score	89% [88, 90]

Additional Safe Use Questions

The survey included additional questions about the safe use of TIRF medicines and prescriber-reported activities performed related to use of TIRF medicines. For a scenario presented of a patient who started on the lowest dose of a TIRF medicine, and after 30 minutes breakthrough pain had not been sufficiently relieved, only 71% of respondents selected the appropriate action (to follow the guidance presented in the product-specific MG). In another scenario, a patient is taking a TIRF medicine and the doctor wants to prescribe a CYP3A4 inhibitor. Eighty percent of respondents identified the appropriate response, that use of TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment, to carefully monitor the patient for opioid toxicity, and combined use can cause fatal respiratory depression. Respondents were aware that if a patient is starting titration with a TIRF medicine, they should start with the lowest available dose (91%). In addition, almost all respondents were aware that TIRF medicine contains fentanyl which can be fatal to children (99%) and all respondents knew to instruct patients never to share their TIRF medicine (100%).

In terms of prescriber-reported activities, most respondents reported always instructing patients not to share TIRF medicines (80%) while 15% did this only with the first prescription:

Responses were relatively low with respondents reported always performing the following activities or performing them only with the first prescription:

- Asking patients about the presence of children in the home (62%; only with first prescription (22%))
- Counseling patients or caregivers that accidental exposure to TIRF medicines by a child may be fatal (71%; only with first prescription (19%))
- Instructing patients to keep TIRF medicines out of reach of children (79%; only with first prescription (15%))
- Instructing patients about proper disposal of any unused or partially used TIRF medicines (67%; only with first prescription (19%))
- Giving patients the MG for their TIRF medicine (44%; only with first prescription (45%)).
- Talk to the patient about the risks and possible side effects of the TIRF medicine (76%; only with first prescription (18%)).
- Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed (53%; only with first prescription (35%)).

Questions about TIRF Medicine REMS Educational Materials

The survey included questions about prescribers' access to educational materials for TIRF medicines. Almost all prescribers reported receiving or having access to the Prescribing Information (97%), and the majority of those reported reading the Prescribing Information (87%). The majority reported receiving or having access to the Medication Guide (MG) (96%) and 92% of those reported reading it. Most respondents reported reviewing the Patient-Prescriber Agreement Form with each patient prescribed TIRF medicines (95%), signing the Patient-Prescriber Agreement Form (98%), and giving a copy of the Patient-Prescriber Agreement Form to the patient (90%).

Summary of Findings

Overall, surveyed prescribers had a high level of knowledge (≥80%) across most of the key risk message questions as in previous assessments, including awareness that TIRF medicines are contraindicated in opioid non-tolerant patients, that TIRF medicines contain fentanyl and have the potential to be abused and that TIRF medicines are not interchangeable with each other. Responses have consistently not reached the 80% knowledge threshold for appropriate use of an around the clock opioid and a TIRF medicine. Overall, most respondents were aware of the correct indications for TIRF medicine, but 22% still reported that chronic non-cancer pain was an approved indication. Respondents that answered incorrectly stated that they prescribe TIRF medicines for conditions including back pain, chronic pain, for reasons such as efficacy, fast acting, and because other medications used have failed. Overall respondents were aware of specific medication/dose for opioid tolerant patients with the exception of 8 mg oral hydromorphone/day (72%) and an equianalgesic dose of another oral opioid (66%). Correct responses ranged from 66% to 96%.

Most prescriber respondents reported reviewing the Patient-Prescriber Agreement with each patient prescribed TIRF medicines (95%), signing it after reviewing it (99%), and giving the patient a copy (90%). This was comparable to patient responses where most patients reported signing a Patient-Prescriber Agreement Form (77%) and receiving a copy of the form (77%). In general, responses were low in terms of prescriber reported behaviors about always conveying risks and how to store medicines. Most patients reported that a healthcare professional did talk about the risks and possible side effects with them (86%) and how to store the medicine (87%).

Only 44% of prescriber respondents reported giving patients the Medication Guide. Most patients reported receiving the Medication Guide from their pharmacist (91%) versus their prescriber (57%).

Reviewer's Comments

A. The survey only had 294 respondents, instead of the proposed 300. The sponsor should make efforts to reach the target sample size for respondents.
B. Only 77% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. In addition, only 77% of respondents were aware that it is incorrect to instruct patients to continue taking their TIRF medicine if they stop taking their around the clock opioid medicine. Knowledge has consistently been low in this area across assessment periods, and ways to improve knowledge in this area should be identified and implemented.
C. DB7: For the review of the comparison of the demographics of the prescriber survey respondents with the overall population of prescribers who prescribed TIRF medicines provided from IMS data, the survey respondents differed from all IMS prescribers by the average times per month they prescribed TIRF medicines within the past six months, gender, medical profession, number of years practicing medicine, and medical specialty. This may bias the results but we do not know in which direction or by how much. We request the following analyses from the sponsor.
    - Submit subgroup analyses stratified by the average times per month they prescribed TIRF medicines within the past six months, gender, medical profession, number of years practicing medicine, and medical specialty, to quantify the impact of these characteristics on knowledge in the survey.
    - Submit a sensitivity analysis predicting the knowledge rate in all prescribers adjusting for these characteristics in your survey (e.g. standardization)
    - Submit the data for us to reproduce your results.

5.7. APPLICANT'S OVERALL CONCLUSION

The TRIG concludes: "*Based on the data available in this TIRF REMS Access program assessment report (program and product utilization statistics, dispensing activity, program infrastructure and performance, noncompliance reporting, and safety surveillance data) the TRIG concludes that there is no indication that the REMS is not meeting its goals. However, the TRIG acknowledges that the data are limited and that FDA has requested further evaluation, as described in the 48-Month FDA Assessment Report Acknowledgement Letter, to determine whether the REMS is meeting its goals*."

6. OTHER OSE DIVISIONS INPUT

The Division of Epidemiology II (DEPI) provided three reviews (see section 4) in response to three separate consults from DRISK. In addition, DPV provided an

analysis of FAERS reports for accidental exposure, off-label, and use of TIRFs in opioid-non-tolerant patients.

7. CONCLUSIONS

7.1. COMPLETENESS OF REPORT

This assessment report is technically complete and addresses all issues outlined in the approved REMS assessment plan.

7.2. ACHIEVEMENT OF THE GOALS OF THE REMS

The **goals** of the TIRF REMS Access program 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

The included surveillance data (spontaneously reported adverse events as well as RADARS data) appear to indicate that for most outcomes assessed, event rates for TIRF products have **increased** over time. In contrast, event rates for the comparator drugs either in most cases indicated either **decreases** over time or much smaller increases than those noted for TIRF products. The small number of events associated with TIRF products in the RADARS Poison Center data produce large fluctuations in the data which may affect the generalizability of this data.

Findings from the June 15, 2017 individual NDA/ANDA submissions of opioid tolerance data indicate that regardless of the type of analysis, the proportion of opioid-non-tolerant patients receiving a TIRF product ranged from 34.6% to 55.4%. Since the proportion of patients receiving TIRFs as calculated by these analyses remains concerning, the **first objective** (prescribing only to appropriate/opioid-tolerant patients) is not being achieved.

The persistency analysis submitted in the May 26, 2016, 48-month REMS assessment report are difficult to interpret due to numerous data analysis issues and thus resulted in the conclusion that it is not possible to tell if the **second objective** (inappropriate TIRF conversions) is being met. The data provided by the TRIG regarding the **third objective** (prevention of accidental exposure) are limited and

thus difficult to interpret, therefore it is not possible to determine whether this objective is being met.

It appears that the 4th objective is partially being met:

- Patients had a high level of knowledge (≥80%) across most of the key risk messages. Respondents were less aware of the correct indication for TIRFs, and unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. Knowledge rates have consistently been low with both of these questions across assessment periods.
- Pharmacists had a high level of knowledge (≥80%) across most of the key risk messages as in previous assessments. However, fewer than 50% correctly stated that chronic non-cancer pain was not an approved indication, and pharmacist respondents were unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. Knowledge has consistently been low in this area across assessment periods.
- Prescribers also had a high level of knowledge (≥80%) across most of the key risk message questions as in previous assessments. However, as in previous assessments, only 65% correctly stated that chronic non-cancer pain was not an approved indication. Respondents that answered incorrectly stated that they prescribe TIRF medicines for conditions including back pain, neuropathic pain, and post-operative pain.

The REMS is not meeting its overall goal or most of the objectives.

7.3. NEED FOR ASSESSMENT PLAN REVISION

Our August 21, 2014 REMS assessment plan revision letter provided the REMS assessment plan for you to utilize. We have determined that your REMS assessment plan needs revision because it would help inform use of TIRF products if it was known both how many patients are dispensed a TIRF prescription during each reporting period as well as the number of mail order and institutional pharmacies dispensing TIRFs each reporting period.

The revised REMS assessment plan must include, but is not limited to the items described at the very end of Section 10 "Comments to Sponsor" of this review.

7.4. REVIEW TEAM CONCLUSION

DRISK, DEPI, DEPI Drug Use, DAAAP, and the Office of Compliance met several times to discuss this conclusion based on the data in the assessment report. The aim of a DRISK REMS assessment review is to determine (1) whether the report is

complete, and (2) whether the REMS is meeting the goal(s). The review team believes the Assessment to be complete but that it is not meeting its overall goal or most of the stated objectives.

8. RECOMMENDATIONS

We recommend the sponsor be sent a REMS Assessment Acknowledgment letter that includes General Comments.

9. COMMENTS FOR THE SPONSOR

Please send the sponsor a **REMS Assessment Acknowledgement letter** (see CST template (COR-SEC901REMS-10) (COR-BLASEC901REMS-10) stating the following:

We found the REMS assessment to be complete and have determined that the REMS is not meeting its overall goal and most of the objectives due to either insufficient data to inform some objectives or data indicating that other objectives are not being met or are only partially being met.

General Comments: Please send the following **General Comments** to the sponsor.

1. Due to the short time frame between providing these comments to you and the due date for the 72 month REMS assessment, you may submit your 7th assessment report no later than **February 28, 2018.**

2. Regarding your submitted RADARS and spontaneous adverse event data:
   a. The assessment report must separate TIRFs by product. Generic products that are the same dosage form as an innovator product may be combined with the innovator product. However, the data for each individual TIRF product should be included in one document showing trends for each product in the class. It will be much easier to assess REMS effectiveness and interpret the surveillance data than when each product is submitted in a separate report.
   b. Use single-product or single-molecule comparators. We recommend oxycodone IR, oxycodone ER, hydromorphone IR, and oxymorphone IR as comparators.
   c. Clarify why the comparison of means model was a better fit to the data than a comparison of trends (page 98 of the report).
   d. The p-values provided are not very meaningful given the large number of tests performed and the small number of events attributed to TIRFs. Focus

interpretations on the magnitude of changes instead of statistical significance. Statistical significance of results should only be incorporated into the interpretations when sufficient power is present.

e. Report case and mention counts for both the pre- and post-REMS periods for all outcomes for TIRF and comparator products.
f. As a sensitivity analysis, limit the Treatment Center Program (TCP) data to the centers that participated in the TCP for the majority of the study period to improve the ability to trend numbers over time.
g. Report the Poison Center results as annual rates rather than quarterly rates to help stabilize the variability due to small numbers of events.
h. Remove the Impaired Health Care Worker Program data as we no longer think that they add value to our understanding of the trends in outcomes of interest.
i. Provide separate results for unintentional exposures in children under 6 years of age to help identify unintentional pediatric exposures.
j. Provide a separate analysis that includes counts and a description of the characteristics of pediatric patients dispensed TIRF products. Include demographic and relevant clinical information, including comorbid conditions, when available. Accidental ingestion and inappropriate use of fentanyl products among pediatric populations is a public health concern. Use of TIRF products in this population may represent inappropriate prescribing, and the Agency needs additional detail to understand this important issue.

3. Findings from the June 15, 2017 individual NDA/ANDA submissions of opioid tolerance data indicate that regardless of the types of analysis performed, the proportion of opioid-non-tolerant patients receiving a TIRF product ranged from a 34.6% to 55.4%. Thus, the proportion of patients receiving TIRFs as calculated by these analyses continues to be of concern. For any subsequent submissions of this type of opioid tolerance analysis:
   a. The TRIG should include only the analysis using the first class-wide fill (as opposed to the first individual product fill). The first class-wide fill likely indicates the patient's first exposure to a TIRF, and thus these are the patients we are most concerned about should they not be opioid-tolerant at the time of initiating a TIRF product.
   b. The data submitted by the TRIG Sponsors are in a format that does not permit a year by year analysis of opioid tolerance. Thus, it is not possible to determine whether the use of TIRFs in opioid non-tolerant patients is increasing or decreasing. The TRIG should provide yearly calculations of opioid tolerance to allow for this evaluation
   c. For both opioid tolerance and product interchange data, you should utilize a data resource that contains data on prescriber instructions, in addition to drug strength and days' supply, to inform TIRF product dose, since dose is

essential to determine opioid tolerance status (as well as the appropriateness of switches between TIRF products).

d. Lastly, we include responses to your October 16, 2017 response to the October 2, 2017, telecon between the FDA and the TRIG, with respect to opioid tolerance data. You plan to:

    I. "… *investigate the difference between the algorithm used in the TRIG analyses and that used by Insys before proceeding with the validation study. The TRIG has investigated several data options for the validation study and has narrowed the selection to the below two choices* [The Henry Ford Health System (HFHS) and Optum's Clinformatics Claims Data and Integrated Claims-EMR Data]."

        1) Within two weeks from receipt of this communication, submit a detailed explanation of the differences between the "Insys algorithm" for opioid tolerance and the TRIG algorithm used for the product-specific opioid tolerance analyses submitted in June 2017.
        2) The TRIG must move forward with the validation study, without delay. If necessary to avoid any further delay, validate both algorithms.
        3) A full validation study in Optum data is not necessary because, as we discussed in the October 2 call, FDA has already initiated a similar investigation of opioid tolerance algorithm validation in Optum databases through the Yale/Mayo Center for Excellence in Regulatory Science and Innovation. The full validation of the opioid tolerance algorithm should be done in a different data source. However, you could do a smaller portability assessment of the algorithm in Optum if that is the data source that you plan to use for the study of adverse events in opioid non-tolerant patients.
        4) The HFHS data source appears to be reasonable. The linked tumor registry has the added advantage of facilitating an analysis of the proportion of patients prescribed TIRFs who have evidence of cancer at the time of TIRF initiation. FDA would be very interested in this information, as it would help provide additional context for the data you are submitting on TIRF use in opioid non-tolerant patients. To help us further assess the suitability of the data source, by February 28, 2018:
            i. provide the number of patients using TIRFs during the proposed validation study period in HFHS and

ii. compare the demographic and clinical characteristics of the TIRF users in HFHS to a geographically diverse sample of US patients who receive TIRFs, such as from a large nationwide claims database.

5) If the number of TIRF recipients in HFHS is insufficient for a robust analysis, provide counts as well as demographic and clinical characteristics of TIRF recipients in an alternate data source.

II. "*…evaluate risks of adverse outcomes in a cohort of patients who initiated TIRF product but did not meet a validated definition of the labeled requirement of opioid tolerance…compared to rates in a comparator population of patients who initiated a TIRF and met a validated definition of opioid tolerance*"

1) The brief outline for the study of adverse events in opioid non-tolerant vs opioid tolerant patients appears appropriate except that the data source does not appear to have both in- and out-of-hospital deaths with which to assess risk of overdose. Ensure that the data source(s) that you choose can be linked to out-of-hospital death and include this information in your protocol.
2) Of the outcomes proposed, fatal and nonfatal overdose are of most concern to the FDA. We are unaware of any claims-based algorithms that have performed acceptably for misuse or abuse.
3) Submit your draft protocol for the study of fatal and non-fatal overdose in opioid non-tolerant versus opioid-tolerant patients starting TIRFs by February 28, 2018.

4. Revise and re-submit your persistency analysis that was initially submitted as a Supplemental Assessment on May 4, 2016. This re-submission should be responsive to the necessary clarifications and explanations noted in Comments a. through d. below. Clearly note/annotate any changes in data analysis or actual data from the originally submitted report. As stated below, non-overlapping definitions must be employed. Additionally, clarify within each table value a) which number represents the numerator, and b) which number represents the denominator.
   a. Many of the numbers and calculations provided in the report are uninterpretable. For example, if a patient is on a second TIRF regimen, that implies he/she switched from a first TIRF regimen. However, this does not appear to have been accounted for in a clear manner, as the numbers do not add up correctly. Further, if 20.5% of patients changed their index TIRF regimen, that implies that 79.5% did not switch their index TIRF regimen.

However, the final sentence indicates that 65-70% of patients changed their TIRF regimen by discontinuing their TIRF regimen. These metrics' lack of clarity, shifting denominators, and the apparently-overlapping definitions employed regarding switches vs. discontinuations vs. changes, render this analysis very difficult to interpret.

b. It is unclear why the persistency analysis excluded patients with only one prescription dispensed. These people only "persisted" through one prescription, and by excluding them, the analysis overestimates persistency. While it would be appropriate to exclude these individuals from a switching analysis, it is inappropriate to exclude them from a persistency analysis.
c. By requiring follow up time in the database after cohort entry, the analysis captures only survivors and will exclude individuals who die after taking fentanyl – either from the condition the drug is treating, or from the drug itself. This approach conditions on the future, and is inappropriate because it introduces survivor bias.
d. As with the opioid tolerance data, utilize a data source that includes prescriber instructions since dose is the primary consideration for determining whether the REMS goal of mitigating inappropriate switching is being met.

5. In our October 2, 2017 telecon with you, we discussed your March 31, 2017 responses regarding your concerns about identifying databases that can provide ED records and accidental childhood poisoning data that are able to provide sufficient data regarding TIRFs. You responded to our discussion on October 16, 2017. We provide comments on your responses here.
   a. We agree with your outline for assessment of accidental poisonings in children in Optum-Humedica data provided that the sample size is sufficient for estimating the incidence of accidental poisonings from TIRFs with a reasonable level of precision. Provide a draft protocol for this study, along with the counts of children ages 0-6 years with evidence of a claim for poisoning by a synthetic opioid, by February 28, 2018. Include in your draft protocol discussion of sample size and precision of estimates.
   b. We agree with your plan for assessing the DIM data for cases of deaths due to accidental poisoning. We look forward to your draft protocol by February 28, 2018.
   c. We look forward to hearing more about your outreach to assess the feasibility of other sources of data for accidental TIRF poisonings in children.

6. Our concerns about the TRIG's REMS compliance program and some administrative processes continue and include the following issues:
   a. The median prescription processing time for a prescription that experienced at least one REMS-related rejection continues to increase over time for both

chain and independent stores. As previously conveyed in the Agency's April 28, 2017 IR to you, as well as the 36-month and 48-month REMS Assessment Acknowledgement Letters (RAAL), we urged the TRIG to investigate and identify the causes of these increasing delays. The Agency also pointed out that because the reasons for REMS-related rejections (PPAF incomplete, PPAF not submitted, prescriber not registered) appear to have remained the same over time, you should further explore this increase in processing times by evaluating a sample of the prescription rejections with the longest processing time to determine if there are any identifiable reasons that could be addressed in the REMS about why processing times continue to increase.

In response to issues raised at the October 2, 2017 telecon between the FDA and TRIG, on October 16, 2017, you stated that you plan "*…to conduct an analysis of prescription processing times for prescriptions that encounter at least one REMS-related rejection over the period October 29, 2014 – October 28, 2017 to evaluate trends over time. In addition to this analysis, TRIG will expand the reporting of these data to FDA to show a more holistic view of overall REMS rejections, which will put into context the overall processing time for all rejected TIRF prescriptions. The updated metrics will be included in the 02FEB2018 submission*."

In such an analysis that you stated on October 16, 2017, that you plan to conduct, clarify whether your use of the term "authorization" is limited to REMS authorizations or dispensing authorizations, because the latter may reflect insurance issues. If delays in dispensing authorization are the cause, further investigate whether such delays due to insurance issues.

Lastly, for patients who were denied a TIRF prescription due to a missing or incomplete PPAF, it is unclear in how many instances did the prescriber complete the PPAF versus simply prescribe an alternative therapy. Provide any data informing this issue because this may be an indicator of a potential access issue.

b. For the 60-month report, you continued to classify a case of PPAF non-compliance as five or more patients enrolled by the prescriber without a complete PPAF on file (greater than 10 working days from the initial enrollment date not on file with the REMS). In the 48-month RAAL, you were told of FDA's concern that these criteria could lead to an under-reporting of PPAF non-compliance, and that you should explore mechanisms to capture lower levels of non-compliance because it is unknown what proportion of PPAF non-compliance is caused by prescribers with these lower levels of non-compliance.

You were again told of the FDA's continued concerns regarding needing five PPAFs to establish one case of non-compliance at the October 2, 2017 telecon. In response, on October 16, 2017, you stated the following: "*The TRIG will reduce the PPAF threshold to flag prescribers for non-compliance based on patients without a PPAF from 5 to 3 patients. The TRIG evaluated the incidents of non-compliance and has determined that the threshold can be lowered to 3 without a large impact to patient access.* Because you did not elaborate further how lowering the number of PPAFs needed for a case on non-compliance to less than 3 would affect patient access, we sent another information request on October 27, 2017 asking for an explanation. In your November 2, 2017 response, you stated that: "*To determine the impact of decreasing the threshold for missing PPAFs triggering a non-compliant event, the TRIG calculated estimated increases in non-compliant case volume based on current prescriber and PPAF activity. At the time of this research, the TRIG found that lowering the threshold to:*

- *4 missing PPAFs would result in 2 additional non-compliant cases per month (~15% increase),*
- *3 missing PPAFs would result in 5 additional non-compliant cases per month (~38% increase),*
- *2 missing PPAFs would result in 14 additional non-compliant cases per month (~107% increase), and*
- *1 missing PPAF would result in 42 additional non-compliant cases per month (~323% increase).*"

In addition, you stated that you considered: "*…the establishment of more strict corrective action guidelines (as proposed in the 16OCT2017 response to FDA), which will result in a higher volume of prescriber suspensions and deactivations* [discussed in comment "c" directly below]. *Therefore, the TRIG proposes that the increase in noncompliant cases by 38% balances the goals of making prescribers aware of the importance of compliance and patient safety without impacting patient access.*"

Given our concerns regarding the high use of TIRFs in opioid non-tolerant patients, as well as continued concerns with the TIRF adverse event data as compared to other opioids, the FDA believes that the number of PPAFs associated with a non-compliance event needs to be set at "one".

Lastly, in your 48-month REMS assessment report, you reported a number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. We stated to you in our November 10, 2016, REMS Assessment Acknowledgement Letter that "It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of

timely completion of PPAFs." In the current REMS assessment report, you state that you "*…will further query noncompliant prescribers to determine more specific reasons of why they were not compliant with the REMS requirements. The TRIG will assess these responses to determine appropriate actions*." The FDA looks forward to reviewing the findings of the TRIG's query and assessment of responses in their subsequent assessment reports.

c. Your current assessment report continues to include cases of prescribers who receive numerous Notices of Violation, Warning Letters, and then file several CAPs before one is accepted. Yet, these prescribers are rarely suspended and apparently never deactivated from the program. In our November 10, 2016, REMS Assessment Acknowledgement Letter, you were asked to add increased specificity to your Non-Compliance Review Team (NCRT) protocol as well as to the Supporting Document of the REMS. Also, at the October 2, 2017 telecon between the FDA and the TRIG you were urged to develop clear and specific criteria to your NCRT non-compliance protocol. In your October 16, 2017, response, you presented the following criteria: "*The Corrective Action Guidelines within the Non-compliance Protocol will be modified to remove the second level of Notices, Warnings and Suspensions, thereby reducing the number of non-compliant events that can occur prior to deactivation of a non-compliant stakeholder, including prescribers. Once non-compliance has been confirmed, the revised non-compliant event schedule will include the following actions.*

    - *A first offense of non-compliance will result in a Notice*
    - *A second offense of non-compliance will result in a Warning*
    - *A third offense of non-compliance will result in a Suspension*
    - *A fourth offense of non-compliance will result in a Deactivation*

    As a result of both changes, a stakeholder, including prescribers, will be deactivated from the program upon four non-compliant events."

    The FDA believes that the TRIG should lower these 4 stages into 3 stages, and that the TRIG should eliminate their first (Notice) stage. Thus the first non-compliance event would be a Warning, the second event would results in a Suspension, and the third would result in a deactivation for a 3-year period.

d. In our November 10, 2016, REMS Assessment Acknowledgement Letter, we expressed concern that all three instances where a non-closed system pharmacy dispensed a TIRF product after a REMS rejection were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The FDA then suggested that the "*TRIG should develop a more active*

mechanism by which to identify and prevent such occurrences". In the current assessment report you state that you are "…*looking into a more active mechanism to identify and prevent instances where a non-closed system pharmacy dispenses a TIRF product after a TIRF REMS rejection is received*." In addition, in response to an April 28, 2017 FDA information request to the TRIG, you verified that you have "…*no way to systematically and accurately track if a pharmacy receives this rejection and still makes the decision to dispense*" and that "*All of these referenced instances would only be captured through spontaneous reports to the TIRF REMS Access program*." It is likely that relying solely on spontaneous pharmacy self-reports of non-compliance will lead to an overall under-reporting in pharmacy non-compliance with the REMS. Develop concrete and more active processes to address this deficiency in your compliance program and implement these processes expeditiously. For example, many pharmacy management systems are able to track when a prescription is picked up by the patient. It may be possible to link the pick-up of a TIRF prescription to earlier data about that prescription where a REMS-edit reject occurred but the pharmacist decided to make the prescription ready for pick-up nonetheless. Present your proposals in your February 2018 assessment report submission.

e. We agree that it may not be practical to convert the two governmental closed pharmacies to a switch system similar to that used by non-closed system pharmacies given the low volume of TIRF prescriptions that are processed by these systems. However, as stated in our November 10, 2016, REMS Assessment Acknowledgement Letter, the TRIG should insist that alternative approaches be taken by the two governmental entities. Examples of such alternatives could include: 1) both entities build in system alerts reminding pharmacists of the REMS requirements; and or 2) request that the two governmental entities develop a process requiring a two-person check when any TIRF is dispensed to ensure that REMS processes were followed. Likely there are additional processes that can be implemented. In the February 28, 2018 assessment report submission, provide an update regarding your consideration of a quarterly evaluation of closed system pharmacy data. These alerts/revised processes should be in place and reported on starting with the December 2018 assessment report..

f. We note in your May 30, 2017 response to our April 28, 2017 information request that your "independent pharmacy" category contains a mix of retail, mail order, and institutional outpatient pharmacies (and thus this category of pharmacies dispenses the bulk of TIRF prescriptions). In order for us to better understand how TIRF products are made available to consumers, research and report what proportion of prescriptions come from each of the

three sub-types of pharmacies contained in your independent pharmacy category and include this in your February 2018 assessment report, as well as all subsequent assessment report submissions.

Additionally, while 48% of the chain stores that became inactivated this reporting period remained inactivated at the end of the reporting period, 77% of independent stores that became inactivated this reporting period remained so at the close of the period. During the previous reporting period, a similar pattern was seen in which a smaller proportion of inactivated chain stores remained inactive at the end of the reporting period (16.6%) as compared to independent pharmacies (78.4%). It is not clear why this large discrepancy exists. Similarly research why this discrepancy exists between these pharmacy types and include this in your February 2018 assessment report.

g. In the 48-month assessment report, 6 inpatient pharmacies either did not respond to the audit request or decided not to participate. In the current assessment report, 3 of 12 pharmacies (25%) did not respond to an audit request and you stated that you are "*…considering revisions to this (pharmacy) enrollment form to allow for process audits so as to increase the potential pool of inpatient pharmacies in the audit and will communicate any required modifications during the review of the next REMS assessment*." The FDA agrees that the TRIG should consider this revision and looks forward to learning of the TRIG's decision regarding this enrollment form.

h. In the February 17, 2017 Supplement to Assessment report submission, you stated that: "*In response to the request from the FDA, a timeline has been developed to perform outreach to a representative sample of those health professional and pharmacies that did not re-enroll in the TIRF REMS Access program to ascertain their reasons for not re-enrolling. The TRIG has initiated activities to collect these data and results will be included in the 72-Month FDA REMS Assessment Report*." The Agency looks forward to reviewing the data regarding the reasons why certain stakeholders chose not to re-enroll in your 72-month Assessment Report. As part of these data to be submitted for the 72-month report, detail whether pharmacy inactivations occurred disproportionately among any particular chain or geographic region.

i. Many of the comments about your compliance program and administrative processes have been raised to you in previous REMS Assessment Acknowledgement Letters, and were again raised in the October 2, 2017 FDA-TRIG teleconference. We expect the above-noted changes/updates to the REMS compliance program/ administrative aspects to be made in the Supporting Document and submitted to the Agency by February 28, 2018.

7. Regarding the patient survey:

a. Respondents were unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine, with only 40% selecting the correct answer. Knowledge rates have consistently been low with these questions across assessment periods and the TRIG should consider how to strengthen the understanding of this message and propose modifications to address this by the February 2018 assessment report submission.
b. For the review of the comparison of the demographics of the patient survey respondents with the overall population of patient who are prescribed TIRF medicines, the survey respondents had a significantly higher "highest education level completed" than all users in the IMS database. Thus, we suspect the knowledge rate in the survey was overestimating the knowledge rate for all users; we request the following analyses from the sponsor in the February 2018 assessment report.
    - Submit subgroup analyses stratified by education level, to quantify the impact of education on knowledge in the survey.
    - Submit a sensitivity analysis predicting the knowledge rate in all users adjusting for education level in your survey (e.g. standardization)
    - Submit the data for us to reproduce your results.

8. Regarding the pharmacist survey:
    a. There was only one closed system pharmacy (CSP) survey respondent. The TRIG should increase efforts to get additional closed systems to participate in the survey.
    b. Only 62% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. In addition, only 41% of respondents were aware that a patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine. Knowledge has consistently been low in this area across assessment periods, and the TRIG should consider how to strengthen the understanding of this message and provide this in the February 2018 assessment report submission.
    c. Only 62% of the inpatient pharmacy respondents reported having an established system, order sets, or protocols to ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access Program. For all inpatient pharmacies that report that they do not have such established systems, conduct outreach to re-educate the authorized person. These inpatient pharmacies should be audited again within 6 months and should be de-enrolled from the program if they are unable to comply. Report on the outreach and follow-up audit in each subsequent assessment report starting with the December 2018 report.
    d. For the review of the comparison of the demographics of the pharmacist survey respondents with the overall population of pharmacists who

prescribed TIRF medicines, the survey respondents differed from all pharmacists in the REMS switch provider data by type of pharmacies. This may bias the results but we do not know in which direction or by how much. We request the following analyses from the TRIG by the February 2018 assessment report submission:

- Submit subgroup analyses stratified by type of pharmacy, to quantify the impact of type of pharmacy on knowledge in the survey.
- Submit a sensitivity analysis predicting the knowledge rate in all pharmacists adjusting for type of pharmacy in your survey (e.g. standardization)
- Submit the data for us to reproduce your results.

9. Regarding the prescriber survey:
   a. The survey only had 294 respondents, instead of the proposed 300. The sponsor should make efforts to reach the target sample size for respondents.
   a. Only 77% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. In addition, only 77% of respondents were aware that it is incorrect to instruct patients to continue taking their TIRF medicine if they stop taking their around the clock opioid medicine. Knowledge has consistently not met the 80% knowledge threshold in this area across assessment periods, and the TRIG should consider how to strengthen the understanding of this message and propose <u>modifications</u> to address this by the February 2018 assessment report submission.
   b. For the review of the comparison of the demographics of the prescriber survey respondents with the overall population of prescriber who prescribed TIRF medicines provided from IMS data, the survey respondents differed from all IMS prescribers by the average times per month TIRF medicines were prescribed within the past six months, gender, medical profession, number of years practicing medicine, and medical specialty. This may bias the results but we do not know in which direction or by how much. We request the following analyses from the TRIG by the February2018 assessment report submission.
      - Submit subgroup analyses stratified by the average times per month TIRF medicines were prescribed within the past six months, gender, medical profession, number of years practicing medicine, and medical specialty, to quantify the impact of these characteristics on knowledge in the survey.
      - Submit a sensitivity analysis predicting the knowledge rate in all prescribers adjusting for these characteristics in your survey (e.g. standardization)
      - Submit the data for us to reproduce your results.

REMS Assessment Plan: Please send the following to communicate the **REMS Assessment Plan Revision** to the TRIG:

Our August 21, 2014 REMS assessment plan revision letter described your REMS assessment plan. We have determined that your REMS assessment plan needs revision because it would help inform use of TIRF products if we knew both how many patients are dispensed a TIRF prescription each reporting period as well as the number of mail order and institutional pharmacies dispensing TIRFs each reporting period.

The REMS assessment plan must include but is not limited to the following items. Additions are noted by **bold underline** and deletions are noted by ~~strikethrough~~.

Modified Assessment Plan for the TIRF REMS

1. The TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively):
   a. Patient Enrollment:
      a. Number of unique patients enrolled
      b. Number of patients inactivated
      c. Number of unique patients dispensed a prescription for a TIRF during this reporting period
   b. Prescriber Enrollment:
      a. Number of prescribers enrolled
      b. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;
      c. Number of prescribers inactivated
   c. Pharmacy Enrollment:
      a. Number of pharmacies enrolled by type (inpatient, chain, independent, **mail order, institutional outpatient, and** closed system; provide identity of closed system entities);
      b. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);
      c. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);
   d. Distributor enrollment:
      a. Number of distributors enrolled;
      b. Number of distributors inactivated;

2. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)

a. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity;
b. Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken);
c. Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons;
d. Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized
e. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF;
f. Number of prescriptions dispensed after ten days without a PPAF in place

3. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

a. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described;
b. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions;
c. Call center report with:
    i. Overall number of contacts;
    ii. Summary of frequently asked questions;
    iii. Summary of REMS-related problems reported
d. Description of corrective actions taken to address program/system problems.

4. TIRF REMS Access Non-Compliance Plan: The TIRF TRIGs should provide the following data regarding non-compliance in each assessment report (per reporting period):

a. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:
    i. Verification of training for all pharmacists dispensing TIRF products;
    ii. Numbers of prescription authorizations per closed system;
    iii. Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to

patients with a valid enrollment in the TIRF REMS program. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).

iv. Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

b. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period These reports are to include:
    i. Verification of training for all pharmacists dispensing TIRF products
    ii. Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program
    iii. Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events
c. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:
    i. Description of how the NCRT defines a non-compliance event
    ii. Description of how non-compliance information is collected and tracked
    iii. Criteria and processes the Team uses to make decisions
    iv. Summary of decisions the Team has made during the reporting period
    v. How the Team determines when the compliance plan should be modified
d. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action
e. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrence
f. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences
g. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified
h. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified
i. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified.

5. Safety Surveillance (data collected per reporting period):

a. TIRF TRIGs will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the TRIG's respective Standard Operating Procedures

b. TIRF TRIGs will produce one comprehensive report that presents spontaneous adverse event data from all TRIGs of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:

   i. Line listings under each category of adverse events of interest as listed above

   ii. Line listings should provide at a minimum the following information (see sample table provided):

      1. Identifying case number
      2. Age and Gender of the patient
      3. Date of the event as well as of the report
      4. The Preferred Terms
      5. Indication of TIRF use
      6. Duration of TIRF therapy
      7. Concomitant medications
      8. Event Outcome

   iii. Other metrics of interest include:

      1. Number of event reports in each event category of interest
      2. Counts of adverse events related to inappropriate conversions between TIRF products
      3. Counts of adverse events related to accidental and unintentional exposures
      4. Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients

   iv. Duplicate cases are identified and eliminated

   v. Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such

   vi. For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

c. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed

below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:

i. Non-medical use of prescription drugs
ii. Surveys conducted at substance abuse treatment programs
iii. College surveys
iv. Poison control center data
~~v. Impaired health care workers~~
vi. Drug-related hospital emergency department visits
vii. Drug-related deaths
viii. Other databases as relevant

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

6. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages.

10. APPENDIX

10.1 ASSESSMENT PLAN

Assessment Plan for TIRF REMS (finalized 8/21/14)

1. The TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively):
   a. Patient Enrollment:
      a. Number of unique patients enrolled
      b. Number of patients inactivated
   b. Prescriber Enrollment:
      a. Number of prescribers enrolled
      b. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;
      c. Number of prescribers inactivated
   c. Pharmacy Enrollment:
      a. Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities);

b. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);
c. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);

d. Distributor enrollment:
   a. Number of distributors enrolled;
   b. Number of distributors inactivated;

7. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)

g. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity;
h. Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken);
i. Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons;
j. Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized
k. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF;
l. Number of prescriptions dispensed after ten days without a PPAF in place

8. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

e. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described;
f. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions;
g. Call center report with:
   iv. Overall number of contacts;
   v. Summary of frequently asked questions;
   vi. Summary of REMS-related problems reported
h. Description of corrective actions taken to address program/system problems.

9. TIRF REMS Access Non-Compliance Plan: The TIRF TRIGs should provide the following data regarding non-compliance in each assessment report (per reporting period):

j. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:
    v. Verification of training for all pharmacists dispensing TIRF products;
    vi. Numbers of prescription authorizations per closed system;
    vii. Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS program. period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).
    viii. Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

k. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period These reports are to include:
    iv. Verification of training for all pharmacists dispensing TIRF products
    v. Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program
    vi. Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events

l. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:
    vi. Description of how the NCRT defines a non-compliance event
    vii. Description of how non-compliance information is collected and tracked
    viii. Criteria and processes the Team uses to make decisions
    ix. Summary of decisions the Team has made during the reporting period
    x. How the Team determines when the compliance plan should be modified

m. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action

n. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrence
o. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences
p. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified
q. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified
r. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified.

10. Safety Surveillance (data collected per reporting period):

d. TIRF TRIGs will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the TRIG's respective Standard Operating Procedures
e. TIRF TRIGs will produce one comprehensive report that presents spontaneous adverse event data from all TRIGs of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:
    i. Line listings under each category of adverse events of interest as listed above
    ii. Line listings should provide at a minimum the following information (see sample table provided):

9. Identifying case number
10. Age and Gender of the patient
11. Date of the event as well as of the report
12. The Preferred Terms
13. Indication of TIRF use
14. Duration of TIRF therapy
15. Concomitant medications
16. Event Outcome

iii. Other metrics of interest include:
    1. Number of event reports in each event category of interest
    2. Counts of adverse events related to inappropriate conversions between TIRF products
    3. Counts of adverse events related to accidental and unintentional exposures

4. Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients

iv. Duplicate cases are identified and eliminated

v. Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such

vi. For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

f. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:

i. Non-medical use of prescription drugs

ii. Surveys conducted at substance abuse treatment programs

iii. College surveys

iv. Poison control center data

v. Impaired health care workers

vi. Drug-related hospital emergency department visits

vii. Drug-related deaths

viii. Other databases as relevant

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

11. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages

10.2 NOVEMBER 10, 2016 REMS ASSESSMENT ACKNOWLEDGEMENT LETTER

1. After review of the 48 month (5th overall) REMS assessment report for the Transmucosal Immediate-Release Fentanyl (TIRF) Products REMS,

we conclude that it is not possible to determine whether the overarching goal of the REMS - to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors is being met.

a. The first objective (prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients) is not being achieved. In the TIRF REMS Industry Group's (TRIG's) assessment of opioid tolerance, approximately 42% of patients prescribed TIRF products were not opioid tolerant. It is important that the TRIG further investigate this issue.
b. It is not possible to determine if the second objective (preventing inappropriate conversion between TIRF medicines) is being met. Though no instances of inappropriate conversions were submitted as a spontaneous report, the persistency analysis provided indicates that the number of patients who may be exposed to inappropriate conversion between TIRF medicines may be as high as 17.1-20.5% of patients receiving TIRF medicines. Further assessment of these findings is also warranted.
c. It is also not possible to determine if the third objective (preventing accidental exposure to children and others for whom it was not prescribed) is being met. The case reports for this metric remain quite low thus challenging the ability to assess the impact of the REMS on this objective, particularly since the case reports do not provide enough information to conduct a root cause analysis (RCA).
d. The fourth objective (educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines) is partially being met. Overall, patients, prescribers, and pharmacists seem to have an adequate understanding of most of the key risk messages related to preventing inappropriate conversion, accidental exposure, and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however, all groups had a lower awareness of the need to only prescribe and dispense TIRF medicines to appropriate patients.

2. In order to address the deficiencies outlined in 1a, b, c, and d, we have the following comments:

a. Regarding the assessment of opioid tolerance submitted in the 48 month assessment, approximately 42% of patients prescribed TIRF products were not opioid tolerant. The TRIG needs to further investigate this concerning finding. A timeline for a plan to further evaluate this finding should be submitted with the February 17, 2017, submission of the 60 month REMS assessment survey results. At a minimum, further evaluation of this finding will include product-specific assessment of opioid tolerance that each member

sponsor will submit only to their NDA or ANDA. Additional details regarding this evaluation will be communicated in a separate letter.

b. Regarding the persistency analysis submitted by the TRIG, these data indicate that the number of patients who may be exposed to "inappropriate conversion between TIRF medicines" is not insignificant. Thus these TIRF product switches need to be further assessed by the TRIG and a protocol developed to assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling. In addition, if the data system used has outcome data, this would be informative as to whether or not any switch marked as "inappropriate" resulted in any adverse sequelae. Limitations of the databases and/or approaches used are to be included in the protocol. Please submit this protocol with the February 17, 2017, submission of the 60 month REMS assessment survey results; if additional time for protocol development is needed, please request an extension.

c. We would like to schedule a meeting to discuss opportunities for obtaining additional data on accidental exposure to children and others for whom TIRF products are not prescribed, as well as to discuss possible ways to address the low awareness of the need to prescribe and dispense TIRF medicines to appropriate patients.

3. Additional comments on the 48-month assessment:

   a. In the FDA's 36-month REMS Assessment Acknowledgement Letter (date August 3, 2015), the TRIG was asked to "*Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues*." In the 48 month assessment report, the TRIG responded that: "*Based on…analysis, there is no barrier to patient access and further outreach is unwarranted*." The TRIG stated that 516 prescribers (8.6%) chose to not re-enroll and that these prescribers had an average of no more than four prescriptions total over the course of the reporting period. However, the reasons why these prescribers withdrew from the program are unknown as are the reasons why 1,134 prescribers had their enrollment expire this reporting period and remain expired. Additionally, the reasons why 412 pharmacies chose not to re-enroll are not presented.

      It is therefore important that the TRIG proceed with conducting an "…outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access

Program so as to ascertain their reasons…(w)e are concerned about potential patient access issues." Submit a timeline for the plan to conduct this outreach in the February 17, 2017, submission of the 60 month REMS assessment survey results. There continues to be a steady increase in mean and median prescription processing times during this reporting period versus the previous periods. The TRIG was previously asked to investigate this finding, but did not do so, instead stating that this finding may be due to a lower number of prescriptions with at least one initial REMS-related rejection this reporting (1,735) period as compared to the 36-month report (3,738). These differences cited by the TRIG do not appear to be so large as to account for some sort of number skewing induced by a small sample size. The TRIG needs to investigate and identify the causes of these increasing delays in prescription processing as these are potential indicators of access barriers.

b. The TRIG Protocol for Corrective Actions for Instances of Non-Compliance contains few concrete criteria or decision trees as to how to deal with episodes of non-compliance. Thus it is unclear to us what types of non-compliance actions would reliably lead to suspension or deactivation. The TRIG should add increased specificity to the Non-Compliance Review Team (NCRT) protocol as well as to the Supporting Document of the REMS. In addition, it is concerning that the TRIG's criteria for an incident of an individual prescriber non-compliance with Patient-Prescriber Agreement Form (PPAF) requirements needs to involve at least "5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date." These criteria would appear to potentially lead to an under-reporting of PPAF non-compliance. The TRIG should explore mechanisms to capture lower levels of non-compliance.

c. Regarding the three instances where a non-closed system pharmacy dispensed a TIRF product after a TIRF REMS rejection, all three reports were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The TRIG should develop a more active mechanism by which to identify and prevent such occurrences.

d. Although results for both governmental (Veteran's Health Administration and Department of Defense) and closed-pharmacy systems appear to have improved from the 36-month audit, they continue to be unsatisfactory. The 36-month REMS Assessment Acknowledgement Letter requested that the TRIG "Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report." The TRIG has

issued the following response: “The TRIG has determined that the current prescription authorization volume for closed system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time.” An absence of complaints does not necessarily mean that a closed pharmacy system process is functioning optimally. These audits are likely one of the best sources of information regarding the performance of these closed-system pharmacies in meeting the REMS requirements. If the TRIG does not favor a novel authorization process for all of the closed-system pharmacies solely due to the poor performance of the governmental entities, the TRIG should propose an outreach to these programs to improve compliance. In addition, the TRIG should be sure to include both governmental entities in the 60-month audit so that their performance in the REMS can continue to be monitored. Lastly, the TRIG presents the process times for prescriptions that have experienced at least one REMS-related rejection. However, data on the overall processing time of a prescription that does not meet with any rejections is unclear. Given that one of the pieces of information solicited during the closed-system audits is “Date and time of each prescription transaction,” this is an excellent opportunity for the TRIG to assess prescription processing times for prescriptions that do not experience any REMS-related rejections. The TRIG should add this component to their closed-system audits.

e. For the Inpatient Pharmacy audits, six inpatient pharmacies either did not respond to the audit request or decided not to participate. In the current inpatient pharmacy enrollment form, the pharmacy only agrees to have their training audited. We are considering revisions to this enrollment form to allow for process audits so as to increase the potential pool of inpatient pharmacies in the audit and will communicate any required modifications during the review of the next REMS assessment.
f. The TRIG reports a number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of timely completion of PPAFs.
g. For subsequent submissions of Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) data that contain CII opioid comparators, expand the CII immediate-release opioid category to include oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen.
h. The Agency has increasing concerns about the use of RADARS data to assess some of the outcomes outlined in the TIRF REMS. Given the limitations of RADARS, the Agency believes that additional data

sources that can track adverse outcomes of interest associated with the TIRF products are necessary, and the TRIG must study intermediate objectives more closely related to the REMS intervention. The FDA proposes a meeting with the TRIG to discuss and explore new approaches to assessing this REMS with the goal of gathering useful information to better understand the impact of the REMS and to improve the program going forward.

4. We refer to the July 21, 2016, FDA electronic communication in which comments on the patient, prescriber, and pharmacist surveys were conveyed based upon the 48 month REMS assessment results. We acknowledge the subsequent agreement between the Agency and the TRIG that the survey results for the 60 month TIRF REMS assessment will be submitted to the Agency on February 17, 2017.

10.3 DESCRIPTION OF SURVEILLANCE DATA

Data Source	Description	Definitions
Spontaneous Adverse Event (AE) Reports	AE reports were combined across TIRF products. Line listings for cases of addiction, overdose, deaths, or pediatric exposures were provided and included information about the case such as age, gender, indication for use, preferred terms, and concomitant medications. The Sponsors counted the number of inappropriate conversions between TIRFs, the number of accidental and unintentional exposures, and the number of non-opioid tolerant AE reports. US cases received by the manufacturer within the study period were included. No additional cases from poison centers or literature review were included. Each Sponsor reviewed the case reports to make a final decision about whether they were true cases via a process that was not described.	Preferred terms used to define each outcome are described below. **Addiction:** intentional drug misuse, drug abuse, drug administered at inappropriate site, inappropriate schedule of drug administration, incorrect dose/dosage administered, accidental exposure to product, dependence, drug dependence (antepartum, postpartum), polysubstance dependence **Overdose:** Accidental overdose, intentional overdose, overdose, prescribed overdose, accidental poisoning **Death:** Accidental death, brain death, cardiac death, death, death neonatal, sudden cardiac death, sudden death, agonal death struggle, apparent death, drug ineffective/death, cardio-respiratory arrest, cardiac arrest, respiratory arrest, foetal death **Pediatric Exposures:** Accidental exposure to product by child, drug administered to patient of inappropriate age, failure of child resistant mechanism for pharmaceutical product In addition to the preferred terms, Sponsors did a text-string search for relevant cases using the following terms: addiction, overdose, drug dependence, death, pediatric exposure, died, fatal, inappropriate, multiple drug overdose, expired, passed away, infant, child, mother, father, accidental, son, daughter, grandmother, grandfather, sister, brother, niece, intentional, nephew, aunt, uncle, mom, pop, dad, inappropriate conversion, non-opioid tolerant. Most of the terms were an alternate method for finding cases of addiction, overdose, death, and pediatric exposures, but these text searches were the primary method for finding cases of inappropriate conversion between TIRFs, and use of TIRFs in non-opioid tolerant patients.

Researched Abuse, Diversion, and Addiction Related Surveillance (RADARS®) System		
Poison Center Program (PCP)	The PCP consists of exposure or information calls from the public or healthcare providers to gain information or advice regarding potentially toxic exposures. In 2015, the PCP included 50 (of 55) poison centers in 48 states across the US, covering over 90% of the US population. Information from the caller is entered into a nationally-standardized electronic health record by trained PC staff. Micromedex is available to the PC staff to identify medications based on physical descriptions provided by callers. Prescription exposures are available down to the product level. Follow-up after an exposure call is done as part of standard procedures to get additional information about outcomes resulting from the exposure, such as death.	**Abuse**: "an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect" **Intentional misuse:** "an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect" **Unintentional therapeutic error:** "an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance" **Unintentional general exposures:** accidental unsupervised ingestions that were not defined as "environmental, occupational, therapeutic error, unintentional misuse, bite/sting, food poisoning, or intentional unknown" **Emergency department visits/hospitalizations:** cases "seen at a healthcare facility and coded as treated, evaluated, and released; admitted to critical care unit; admitted to noncritical care unit; admitted to psychiatric care facility" **Deaths:** one of the medical outcomes identified via PCP personnel follow-up of exposure calls **Major medical outcomes and deaths:** deaths and patients who "exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement"
Treatment Center Program (TCP)	The TCP consists of patients seeking treatment for opioid dependence. This program combines two treatment programs; the Opioid Treatment Program (OTP) that collects data from patients entering federally-funded medication-assisted treatment (MAT) centers and the Survey of Key Informants' Patients (SKIP) Program that collects data from patients	**Abuse:** past 30 day endorsement of use of an identified product to get high

	entering non-MAT, mostly privately-funded substance use programs. Both programs use the same data collection instruments to capture past month abuse of specific opioids. Patients are offered the opportunity to voluntarily complete a standardized, anonymous self-administered questionnaire about the opioids that they used in the past 30 days to get high. Patients report primary opioid of abuse (by product), other opioids used, and route of administration (for each drug used in the past month to get high). In 2015 OTP included 68 methadone treatment programs in 40 states and the SKIP included 131 treatment programs covering 47 states.	
College Survey Program (CSP)	The CSP collects anonymous information on past 90-day non-medical (i.e., abuse or misuse) use of prescription drugs from self-identified college students at 2- or 4-year colleges, universities, or technical schools. Self-administered online questionnaires are filled out at the end of the fall, spring, and summer semesters/quarters. The target for number of completed surveys each semester is 2000, and enrollment is stratified into four Census regions. The selection of students is done via a nationwide panel company. No other information was provided about how students are selected for participation. Students can receive prizes for completing these surveys.	Abuse: past 90-day endorsement of non-medical use of an identified product
Impaired Health Care Worker Program (IHWP)	The IHWP is made up of data from the three different programs combined into one dataset: 1) Drug Diversion Program, 2) the PCP, and 3) the TCP. 1. Health care workers that are involved in diverting prescription opioids are identified from reports from regulatory agencies as well as medical, pharmacy, nursing, and dental boards from the Drug Diversion Program. 2. Reports about exposures to opioids in health care workers are identified from the PCP. 3. Health care workers who abused opioids in the past 30 days are identified from the TCP.	Abuse by a health care worker was defined by virtue of identification in the dataset.

10.4 SURVEILLANCE DATA RESULTS

10.4.1. Spontaneous Adverse Event Reports Results[a]

Data Source	Main Findings	Strengths/Limitations	Are these data useful? If yes, are modifications needed?
Spontaneous adverse event (AE) reports 60-month report observation period: 8/29/2015-8/28/2016	Counts and rates for main AEs of interest across three reporting periods (60-month, 48-month, and 36 month) are provided 353 total AEs of interest from MedWatch reports during 60-month reporting period. 344 deaths which far exceeded number of addiction, overdose, or pediatric exposure cases (< 7 cases per AE). No inappropriate conversions, unintentional exposures, or non-opioid tolerant cases. Details for case reports: • Of 6 addiction cases, 1 resulted in death, 3 had unknown outcomes, and 2 had outcome of 'not recovered/resolved'. • Of 344 deaths, 121 were determined to be unrelated to the TIRF medication. Causality could not be determined in about 200 deaths. 4 deaths possibly related to TIRFs and 1 death from an inappropriate use of TIRFs. • Indications other than cancer pain noted among deaths: pain (7), breakthrough pain not specified as cancer pain (7), headaches (1), use prior to dressing changes (1), lung disease (1), chronic pain (3), invertebral disc degeneration (1), sickle cell anemia (1), neck/back pain (4), pain in hip (1), unapproved indication (1), interstitial cystitis (1), sprain of septal cartilage of nose (1), and Crohn's disease (1). Indication was unknown for 179 cases. • 4 overdose cases resulted in 3 deaths. • 3 pediatric cases were from intentional use of TIRFs. Outcomes for 2 cases unknown and third case had outcome of 'not recovered/resolved'.	• Cannot use spontaneous reports to measure or trend incidence/prevalence of AEs. • Minimal case summaries or details provided. For example, the indication for the TIRF was unknown in a majority of deaths.	• May have some utility for ongoing surveillance if further detail on cases, particularly fatal cases, can be provided. For example, identifying numerous severe outcomes that occur in patients using TIRFs for non-cancer pain may indicate a need for further regulatory action. • These data do not appear to be especially useful for assessing whether the REMS is effective.

a Rates of adverse events discussed here encompass the counts of the specific adverse event from divided by 1) the population size from US Census data, 2) the number of prescription fills from IMS Health data, or 3) the number of dosage units from IMS Health data.

10.4.2. Poison Center Program Data[a]

Data Source	Main Findings	Strengths/Limitations	Are these data useful? If yes, are modifications needed?
Poison Center Program (PCP) 60-month report observation period: 10/29/2015-10/28/2016	(b) (4)	• Near-national census of poison center exposure calls. • Misclassification of exposure is thought to be an issue for many solid dosage forms, but it may not be as much of an issue for TIRFs given the unique dosage forms (Table 1). • Numbers of events were extremely low for TIRFs so variability in rates made interpretation of trends difficult. • Poison center calls represent a tiny fraction of events of interest. We don't know what fraction or if it varies over time or across products. In many situations, particularly in the most severe cases, exposed patients may go directly to an emergency department rather than initiating a poison center	• These data may be most useful for monitoring pediatric (<6 years of age) unintentional exposures, but we can continue to monitor other outcomes for consistency with other data sources. • The unintentional outcomes can be reported for children under 6 years of age separately from cases ages 6 years and older. • Rates per prescription may be the most useful for comparing these products. Consider dropping the dosage unit-based rates. • P-values are not needed for surveillance purposes, and they are not very meaningful given the large numbers of tests performed and the small numbers of events for TIRFs. • Case/mention counts in the pre- and post-REMS

(b) (4)		call	period should be provided for all evaluations. • The large groupings of products within the TIRFs and composite comparators may be masking patterns for individual drugs. Instead, single-molecule comparators like oxycodone IR, oxycodone ER, hydromorphone IR, and oxymorphone IR could be used, and TIRFs should be provided by product. • Because of small numbers of cases, annual adverse event rates may be more useful when conducting surveillance over time.

a Rates of adverse events discussed here encompass the counts of the specific adverse event from PCP data divided by 1) the population size from US Census data, 2) the number of prescription fills from IMS Health data, or 3) the number of dosage units from IMS Health data.

10.4.3. Treatment Center Program Results[a]

Data Source	Main Findings	Strengths/Limitations	Are these data useful? If yes, are modifications needed?
Treatment Center Program (TCP) 60-month report observation period: 10/29/2015-10/28/2016 • Survey of Key Informants' Patients (SKIP) • Opioid Treatment Program (OTP)	(b) (4)	• These are convenience samples of people entering opioid treatment. Changes in prevalence do not account for potential changes in the number of individuals accessing treatment. • Generalizability to populations not entering treatment for opioid use disorder is unknown. • Geographic distribution of sample changes over time so a sensitivity analysis is needed using a set of sites that contributed data consistently (e.g., >75% of quarters). • Misclassification of the specific product abused is an issue with these data – unclear how accurately people report abuse of different products within a class, especially generic products, whether patients might just report fentanyl, in general, rather than a specific product name, or how much misclassification may be introduced due to illicit fentanyl. On the other hand, misclassification of exposure may be less for TIRFs than for	• May be useful for comparing abuse rates by product, but generalizability will be limited to those entering treatment for opioid use disorder. • P-values are not needed for surveillance purposes, and they are not very meaningful given the large numbers of tests performed and the small numbers of events for TIRFs. • Abuse rates per prescription may be the most useful for comparing these products. Consider dropping the dosage unit-based rates. • Case/mention counts in the pre- and post-REMS period should be provided for all evaluations. • The large groupings of products within the TIRFs and composite comparators may be masking patterns for individual drugs. Instead, single-molecule comparators like oxycodone IR, oxycodone ER, hydromorphone IR, and oxymorphone IR could be used, and TIRFs should be provided by product.

		other opioid products given the unique dosage forms.	

a Abuse rates discussed here encompass the counts of patients reporting abuse of the product group from TCP data divided by 1) the population size from US Census data, 2) the number of prescription fills from IMS Health data, or 3) the number of dosage units from IMS Health data.

10.4.4. College Survey Program Results[a]

Data Source	Main Findings	Strengths/Limitations	Are these data useful? If yes, are modifications needed?
College Survey Program (CSP) 60-month report observation period: 10/29/2015-10/28/2016	(b) (4)	• Opioid abuse trends in this survey, in general, conflict with findings in other data sources. For example, these survey results suggested that trends in non-medical use for all opioids were increasing, but the TCP data suggested that only TIRFs and schedule 2 opioids increased in the pre- to post-REMS comparison. • Internet survey with unclear sampling frame, survey not validated. We suspect quality of these data are low.	• Despite limitations, these data suggest that there may be an increasing trend towards abuse of TIRFs among college students. The data source may still be useful for evaluating the effectiveness of the REMS and for surveillance with the recommended modifications, below. • P-values are not needed for surveillance purposes, and they are not very meaningful given the large numbers of tests performed and the small numbers of events for TIRFs. • Case/mention counts in the pre- and post-REMS period should be provided for all evaluations. • The large groupings of products within the TIRFs and composite comparators may be masking patterns for individual drugs. Instead, single-molecule comparators like oxycodone IR, oxycodone ER, hydromorphone IR, and oxymorphone IR could be used, and TIRFs should be provided by product.

a The rates discussed here encompass the counts of patients reporting non-medical use of the product group from CSP data divided by 1) the population size from US Census data, 2) the number of prescription fills from IMS Health data, or 3) the number of dosage units from IMS Health data.

10.4.5. Impaired Health Care Worker Program Results[a]

Data Source	Main Findings	Strengths/Limitations	Are these data useful? If yes, are modifications needed?
Impaired Health Care Worker Program (IHWP) 60-month period: 10/29/2015-10/28/2016	(b) (4)	• This type of diversion likely happening through channels unrelated to prescriber education (supply chain diversion rather than diversion of dispensed prescriptions) so it's unable to measure the effectiveness of the REMS.	• Data are probably not useful going forward.

a Rates discussed here encompass the counts of health care workers reporting abuse of the product group from IHWP data divided by 1) the population size from US Census data, 2) the number of prescription fills from IMS Health data, or 3) the number of dosage units from IMS Health data.

10.5. PATIENT SURVEY TABLES

Table 10.5.1: Patients'/Caregivers' Understanding of Key Risk Message 1

Question	12 Month Survey N=192	24 Month Survey N=302	36 Month Survey N=229	48 Month Survey N=310	60 Month Survey N=310
TIRF medicines can cause life-threatening breathing problems that can lead to death.	**True: 173 (90%)** False: 5 (3%) I don't know: 14 (7%)	**True: 272 (90%)** False: 0 (0%) I don't know: 30 (10%)	**True: 209 (91%)** False: 1 (0.4%) I don't know: 19 (8%)	**True: 285 (92%)** False: 3 (1%) I don't know: 22 (7%)	**True: 284 (92%)** False: 8 (3%) I don't know: 18 (6%)
Composite Score	**90%**	**90%**	**91%**	**92%**	**92%**

Table 10.5.2: Patients'/Caregivers' Understanding of Key Risk Message 2

Question	12 Month Survey N=192	24 Month Survey N=302	36 Month Survey N=229	48 Month Survey N=310	60 Month Survey N=310
TIRF medicines should only be taken by patients who are opioid tolerant. *Changed to TIRF medicines should only be taken by cancer patients who are opioid tolerant. (48 month)	**True: 174 (91%)** False: 5 (3%) I don't know: 13 (7%)	**True: 277 (92%)** False: 5 (2%) I don't know: 20 (7%)	**True: 195 (85%)** False: 6 (3%) I don't know: 28 (12%)	***True: 135 (44%)** False: 122 (39%) I don't know: 53 (17%)	**True: 277 (89%)** False: 8 (3%) I don't know: 25 (8%)

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: 176 (90%)** False: 7 (4%) I don't know: 9 (5%)	**True: 267 (88%)** False: 12 (4%) I don't know: 23 (8%)	**True: 187 (82%)** False: 19 (8%) I don't know: 23 (10%)	**True: 280 (90%)** False: 14 (5%) I don't know: 16 (5%)	**True: 273 (88%)** False: 14 (5%) I don't know: 23 (7%)
Composite Score	**61.5%**	**60%**	**54%**	**42%**	**83%**

Table 10.5.3: Patients'/Caregivers' Understanding of Key Risk Message 3

Question	**12 Month Survey N=192**	**24 Month Survey N=302**	**36 Month Survey N=229**	**48 Month Survey N=310**	**60 Month Survey N=310**
For which of the following conditions should you use a TIRF medicine?					
Headache or migraine pain	Yes: 29 (15%) **No: 140 (73%)** I don't know: 23 (12%)	Yes: 25 (8%) **No: 234 (77.5%)** I don't know: 43 (14%)	Yes: 25 (11%) **No: 179 (78%)** I don't know: 25 (11%)	Yes: 32 (10%) **No: 250 (81%)** I don't know: 28 (9%)	Yes: 34 (11%) **No: 242 (78%)** I don't know: 34 (11%)
Breakthrough pain from cancer	**Yes: 134 (70%)** No: 52 (27%) I don't know: 6 (9%)	**Yes: 194 (64%)** No: 90 (30%) I don't know: 18 (6%)	**Yes: 151 (66%)** No: 71 (31%) I don't know: 7 (3%)	**Yes: 212 (68%)** No: 80 (26%) I don't know: 18 (6%)	**Yes: 225 (73%)** No: 81 (26%) I don't know: 4 (1%)
Dental pain	Yes: 3 (2%) **No: 172 (90%)** I don't know: 17 (9%)	Yes: 49 (3%) **No: 264 (87%)** I don't know: 29 (10%)	Yes: 3 (1%) **No: 200 (87%)** I don't know: 26 (11%)	Yes: 8 (3%) **No: 280 (90%)** I don't know: 22 (7%)	Yes: 5 (2%) **No: 269 (87%)** I don't know: 36 (12%)

Pain after surgery 12 month: Acute or post-operative pain	Yes: 40 (21%) **No: 120 (68%)** I don't know: 22 (11%)	Yes: 52 (17%) **No: 207 (68.5%)** I don't know: 43 (14%)	Yes: 44 (19%) **No: 161 (70%)** I don't know: 24 (11%)	Yes: 65 (21%) **No: 210 (68%)** I don't know: 35 (11%)	Yes: 69 (22%) **No: 199 (64%)** I don't know: 42 (14%)
Long-lasting painful conditions not caused by cancer 12 month: chronic non-cancer pain	Yes: 136 (71%) **No: 47 (24%)** I don't know: 9 (5%)	Yes: 210 (69%) **No: 66 (21%)** I don't know: 26 (9%)	Yes: 150 (65.5%) **No: 58 (25%)** I don't know: 21 (9%)	Yes: 135 (44%) **No: 136 (44%)** I don't know: 39 (13%)	Yes: 148 (48%) **No: 121 (39%)** I don't know: 41 (13%)
A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine	**True: 82 (43%)** False: 47 (24.5%) I don't know: 63 (33%)	**True: 103 (34%)** False: 87 (29%) I don't know: 112 (37%)	**True: 84 (37%)** False: 58 (25%) I don't know: 87 (38%)	**True: 122 (39%)** False: 93 (30%) I don't know: 95 (31%)	**True: 123 (40%)** False: 88 (28%) I don't know: 99 (32%)
It is OK for patients to take TIRF medicines for headache pain.	True: 17 (9%) **False: 136 (71%)** I don't know: 39 (20%)	True: 21 (7%) **False: 206 (68%)** I don't know: 75 (25%)	True: 16 (7%) **False: 159 (69%)** I don't know: 54 (24%)	True: 20 (7%) **False: 232 (75%)** I don't know: 58 (19%)	True: 20 (7%) **False: 209 (67%)** I don't know: 81 (26%)
TIRF medicines should be taken exactly as prescribed by the doctor.	**True: 192 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 301 (100%)** False: 0 (0%) I don't know: 1 (0.3%)	**True: 227 (99%)** False: 2 (1%) I don't know: 0 (0%)	**True: 310 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 309 (100%)** False: 1 (<1%) I don't know: 0 (0%)
It is ok to take TIRF medicines for short-term pain that will go away in a few days.	True: 10 (5%) **False: 158 (82%)** I don't know: 24 (13%)	True: 15 (5%) **False: 252 (83%)** I don't know: 35 (12%)	True: 12 (5%) **False: 190 (83%)** I don't know: 27 (12%)	True: 13 (4%) **False: 267 (86%)** I don't know: 30 (10%)	True: 9 (3%) **False: 264 (85%)** I don't know: 37 (12%)
Composite Score	**39%**	**31%**	**32%**	**16%***	**11%***

*Questions added to risk message in 48-month survey

Table 10.5.4.: Patients'/Caregivers' Understanding of Key Risk Message 4

Question	**12 Month Survey N=192**	**24 Month Survey N=302**	**36 Month Survey N=229**	**48 Month Survey N=310**	**60 Month Survey N=310**
It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	True: 1 (0.5%) **False: 186 (97%)** I don't know: 5 (3%)	True: 8 (3%) **False: 285 (94%)** I don't know: 9 (3%)	True: 2 (1%) **False: 222 (97%)** I don't know: 5 (2%)	True: 5 (2%) **False: 295 (95%)** I don't know: 10 (3%)	True: 6 (2%) **False: 297 (96%)** I don't know: 7 (2%)
Composite Score	**97%**	**94%**	**97%**	**95%**	**96%**

Table 10.5.5.: Patients'/Caregivers' Understanding of Key Risk Message 5

Question	**12 Month Survey N=192**	**24 Month Survey N=302**	**36 Month Survey N=229**	**48 Month Survey N=310**	**60 Month Survey N=310**
A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	True: 0 (0%) **False: 192 (100%)** I don't know: 0 (0%)	True: 5 (2%) **False: 296 (98%)** I don't know: 1 (0.3%)	True: 1 (0.4%) **False: 227 (99%)** I don't know: 1 (0.4%)	True: 0 (0%) **False: 308 (99%)** I don't know: 2 (1%)	True: 6 (2%) **False: 303 (98%)** I don't know: 1 (<1%)
Selling or giving away TIRF medicines is against the law.	**True: 188 (98%)** False: 3 (2%) I don't know: 1 (0.5%)	**True: 297 (98%)** False: 2 (1%) I don't know: 3 (1%)	**True: 227 (99%)** False: 1 (0.4%) I don't know: 1 (0.4%)	**True: 306 (99%)** False: 2 (1%) I don't know: 2 (1%)	**True: 308 (99%)** False: 1 (<1%) I don't know: 1 (<1%)

A side effect of TIRF medicines is the chance of abuse or addiction.	**N/A**	**N/A**	**N/A**	**N/A**	**True: 287 (93%)** False: 5 (2%) I don't know: 18 (6%)
TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	**N/A**	**N/A**	**N/A**	**N/A**	**True: 302 (97%)** False: 0 (0%) I don't know: 8 (3%)
TIRF medicines should be kept in a safe place to prevent it from being stolen.	**N/A**	**N/A**	**N/A**	**N/A**	**True: 308 (99%)** False: 1 (<1%) I don't know: 1 (<1%)
Composite Score	**98%**	**96%**	**98%**	**98%**	**88%**

Table 10.5.6.: Patients'/Caregivers' Understanding of Key Risk Message 6

Question	**12 Month Survey N=192**	**24 Month Survey N=302**	**36 Month Survey N=229**	**48 Month Survey N=310**	**60 Month Survey N=310**
TIRF medicines should be stored in a safe place out of reach of children.	**True: 192 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 302 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 227 (99%)** False: 1 (0.4%) I don't know: 1 (0.4%)	**True: 309 (100%)** False: 1 (<1%) I don't know: 0 (0%)	**True: 310 (100%)** False: 0 (0%) I don't know: 0 (0%)
TIRF medicines must be disposed of as described in the specific product's Medication Guide	**True: 184 (96%)** False: 2 (1%) I don't know: 6 (3%)	**True: 285 (94%)** False: 0 (0%) I don't know: 17 (6%)	**True: 215 (94%)** False: 1 (0.4%) I don't know: 19 (8%)	**True: 299 (97%)** False: 2 (1%) I don't know: 9 (3%)	**True: 303 (98%)** False: 2 (1%) I don't know: 5 (2%)

A TIRF medicine can cause an overdose and death in any child who takes it.	**True: 174 (91%)** False: 4 (2%) I don't know: 14 (7%)	**True: 275 (91%)** False: 2 (1%) I don't know: 25 (8%)	**True: 209 (91%)** False: 2 (1%) I don't know: 20 (9%)	**True: 289 (93%)** False: 2 (1%) I don't know: 19 (6%)	**True: 292 (94%)** False: 5 (2%) I don't know: 13 (4%)
What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine?	**Get emergency help right away: 171 (89%)** Do nothing: 0 (0%) Wait an hour and see if the person is OK: 6 (3%) I don't know: 15 (8%)	**Get emergency help right away: 264 (87%)** Do nothing: 17 (6%) Wait an hour and see if the person is OK: 2 (1%) I don't know: 19 (6%)	**Get emergency help right away: 202 (88%)** Do nothing: 0 (0%) Wait an hour and see if the person is OK: 7 (3%) I don't know: 20 (9%)	**Get emergency help right away: 273 (88%)** Do nothing: 1 (0%) Wait an hour and see if the person is OK: 6 (2%) I don't know: 30 (10%)	**Get emergency help right away: 276 (89%)** Do nothing: 0 (0%) Wait an hour and see if the person is OK: 10 (3%) I don't know: 24 (8%)
Composite Score	**79%**	**78.5%**	**77%**	**81%**	**84%**

Table 10.5.7.: Patients'/Caregivers' Understanding of Safe Use Questions

Question	**12 Month Survey** **N=192**	**24 Month Survey** **N=302**	**36 Month Survey** **N=229**	**48 Month Survey** **N=310**	**60 Month Survey** **N=310**
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?	**Yes: 165 (86%)** No: 23 (12%) I don't know: 4 (2%)	**Yes: 259 (86%)** No: 36 (12%) I don't know: 7 (2%)	**Yes: 200 (87%)** No: 23 (10%) I don't know: 6 (3%)	**Yes: 259 (84%)** No: 36 (12%) I don't know: 15 (5%)	**Yes: 265 (86%)** No: 37 (12%) I don't know: 3 (5%)

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?	Yes: 180 (94%) No: 12 (6%) I don't know: 0 (0%)	Yes: 281 (93%) No: 19 (6%) I don't know: 2 (1%)	Yes: 241 (93%) No: 13 (6%) I don't know: 21 (9%)	Yes: 296 (96%) No: 9 (3%) I don't know: 5 (2%)	Yes: 294 (95%) No: 15 (5%) I don't know: 1 (<1%)
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: 155 (81%) No: 33 (17%) I don't know: 4 (2%)	Yes: 241 (80%) No: 52 (17%) I don't know: 9 (3%)	Yes: 185 (81%) No: 38 (17%) I don't know: 6 (3%)	Yes: 255 (82%) No: 49 (16%) I don't know: 6 (2%)	Yes: 270 (87%) No: 35 (11%) I don't know: 5 (2%)
TIRF medicines are only available to patients through a special program (called the TIRF REMS Access Program).	**True: 97 (51%)** False: 23 (12%) I don't know: 72 (37%)	**True: 147 (49%)** False: 33 (11%) I don't know: 122 (40%)	**True: 162 (71%)** False: 9 (4%) I don't know: 58 (25%)	**True: 236 (76%)** False: 8 (3%) I don't know: 66 (21%)	**True: 238 (77%)** False: 10 (3%) I don't know: 62 (20%)

10.6. Pharmacist Survey Tables

Table 10.6.1.: Pharmacists' Understanding of Key Risk Message 1

Question	12 Month Survey N=302	24 Month Survey N=300	36 Month Survey N=300	48 Month Survey N=301	60 Month Survey N=318
According to the labeling, patients considered opioid-tolerant are those: (12-month and 60-month) According to labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: (24, 36, and 48 month)					
Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	**True: 38 (13%)** False: 255 (84%) I don't know: 9 (3%)	**True: 271 (90%)** False: 23 (8%) I don't know: 6 (2%)	**True: 281 (94%)** False: 11 (4%) I don't know: 8 (3%)	**True: 279 (93%)** False: 22 (7%) I don't know: 0 (0%)	**True: 304 (96%)** False: 10 (3%) I don't know: 4 (1%)
Who are not currently taking opioid therapy, but have taken opioid therapy before.	True: 46 (15%) **False: 242 (80%)** I don't know: 14 (5%)	True: 41 (14%) **False: 242 (81%)** I don't know: 17 (6%)	True: 29 (10%) **False: 261 (87%)** I don't know: 10 (3%)	True: 9 (27%) **False: 263 (87%)** I don't know: 11 (4%)	True: 30 (9%) **False: 278 (87%)** I don't know: 10 (3%)
Who have no known contraindications to the drug fentanyl, but are not currently taking around-the clock opioid therapy **12 month**: Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	True: 242 (80%) **False: 47 (16%)** I don't know: 13 (4%)	True: 52 (17%) **False: 228 (76%)** I don't know: 20 (7%)	True: 44 (15%) **False: 236 (79%)** I don't know: 20 (7%)	True: 44 (15%) **False: 248 (82%)** I don't know: 9 (3%)	True: 46 (15%) **False: 261 (82%)** I don't know: 11 (4%)
TIRF medicines are contraindicated in opioid non-tolerant patients because life-	**True: 260 (86%)** False: 24 (8%)	**True: 258 (86%)** False: 27 (9%)	**True: 271 (91%)** False: 19 (6%)	**True: 274 (91%)** False: 19 (6%)	**True: 281 (88%)** False: 23 (7%)

threatening respiratory depression could occur at any dose.	I don't know: 18 (6%)	I don't know: 15 (5%)	I don't know: 9 (3%)	I don't know: 8 (3%)	I don't know: 14 (4%)
Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**True: 278 (92%)** False: 5 (2%) I don't know: 19 (6%)	**True: 281 (94%)** False: 2 (1%) I don't know: 17 (6%)	**True: 281 (94%)** False: 4 (1%) I don't know: 15 (5%)	**True: 287 (95%)** False: 4 (1%) I don't know: 10 (3%)	**True: 303 (95%)** False: 3 (1%) I don't know: 12 (4%)
TIRF medicines may be used in opioid non-tolerant patients.	True: 48 (16%) **False: 237 (78.5%)** I don't know: 17 (6%)	True: 40 (13%) **False: 246 (82%)** I don't know: 14 (5%)	True: 39 (13%) **False: 251 (84%)** I don't know: 10 (3%)	True: 35 (12%) **False: 257 (85%)** I don't know: 9 (3%)	True: 28 (9%) **False: 278 (87%)** I don't know: 12 (4%)
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: 237 (78.5%)** False: 46 (15%) I don't know: 19 (6%)	**True: 248 (83%)** False: 38 (13%) I don't know: 14 (5%)	**True: 237 (79%)** False: 50 (17%) I don't know: 13 (4%)	**True: 243 (81%)** False: 45 (15%) I don't know: 13 (4%)	**True: 267 (84%)** False: 34 (11%) I don't know: 17 (5%)
According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:					
8 mg oral hydromorphone/day	**N/A**	**True: 237 (79%)** False: 29 (10%) I don't know: 34 (11%)	**True: 229 (76%)** False: 31 (10%) I don't know: 40 (13%)	**True: 237 (79%)** False: 30 (10%) I don't know: 13 (4%)	**True: 237 (75%)** False: 38 (12%) I don't know: 43 (14%)
60 mg oral morphine/day	**N/A**	**True: 255 (85%)** False: 14 (5%) I don't know: 31 (10%)	**True: 253 (85%)** False: 15 (5%) I don't know: 31 (10%)	**True: 270 (90%)** False: 11 (4%) I don't know: 20 (7%)	**True: 280 (88%)** False: 13 (4%) I don't know: 25 (8%)

30 mg oral oxycodone/day	**N/A**	**True: 214 (71%)** False: 44 (15%) I don't know: 42 (14%)	**True: 220 (73%)** False: 38 (13%) I don't know: 42 (14%)	**True: 232 (77%)** False: 41 (14%) I don't know: 28 (9%)	**True: 247 (78%)** False: 37 (12%) I don't know: 34 (11%)
25 mcg transdermal fentanyl/hour	**N/A**	**True: 216 (72%)** False: 45 (15%) I don't know: 39 (13%)	**True: 223 (74%)** False: 31 (10%) I don't know: 46 (15%)	**True: 232 (77%)** False: 42 (14%) I don't know: 27 (9%)	**True: 253 (80%)** False: 39 (12%) I don't know: 26 (8%)
25 mg oral oxymorphone/day	**N/A**	**True: 213 (71%)** False: 29 (10%) I don't know: 58 (19%)	**True: 213 (71%)** False: 26 (9%) I don't know: 61 (20%)	**True: 221 (73%)** False: 36 (12%) I don't know: 44 (15%)	**True: 229 (72%)** False: 30 (9%) I don't know: 59 (19%)
An equianalgesic dose of another oral opioid	**N/A**	**True: 177 (59%)** False: 61 (20%) I don't know: 62 (21%)	**True: 177 (59%)** False: 57 (19%) I don't know: 66 (22%)	**True: 196 (65%)** False: 49 (16%) I don't know: 56 (19%)	**True: 207 (65%)** False: 51 (16%) I don't know: 60 (19%)
Composite Score	**57%***	**43%**	**50%**	**30%**	**31%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

Table 10.6.2.: Pharmacists' Understanding of Key Risk Message 2

Question	**12 Month Survey N=302**	**24 Month Survey N=300**	**36 Month Survey N=300**	**48 Month Survey N=301**	**60 Month Survey N=318**

According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	N/A	True: 80 (27%) **False: 196 (65%)** I don't know: 24 (8%)	True: 85 (28%) **False: 190 (63%)** I don't know: 25 (8%)	True: 70 (23%) **False: 208 (69%)** I don't know: 23 (8%)	True: 82 (26%) **False: 197 (62%)** I don't know: 39 (12%)
According to the product labeling, a cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	N/A	True: 50 (17%) **False: 224 (75%)** I don't know: 26 (9%)	True: 57 (19%) **False: 222 (74%)** I don't know: 21 (7%)	True: 37 (12%) **False: 247 (82%)** I don't know: 17 (6%)	True: 34 (11%) **False: 256 (81%)** I don't know: 28 (9%)
A patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine	N/A	N/A	N/A	**True: 126 (42%)** False: 136 (45%) I don't know: 39 (13%)	**True: 131 (41%)** False: 151 (48%) I don't know: 36 (11%)
Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?					
Acute or postoperative pain	Yes: 52 (17%) **No: 236 (78%)** I don't know: 14 (5%)	Yes: 31 (10%) **No: 254 (85%)** I don't know: 15 (5%)	Yes: 33 (11%) **No: 260 (87%)** I don't know: 7 (2%)	Yes: 22 (7%) **No: 271 (90%)** I don't know: 8 (3%)	Yes: 35 (11%) **No: 273 (86%)** I don't know: 10 (3%)
Headache or migraine pain	Yes: 12 (4%) **No: 269 (89%)** I don't know: 21 (7%)	Yes: 8 (3%) **No: 277 (92%)** I don't know: 15 (5%)	Yes: 9 (3%) **No: 272 (91%)** I don't know: 19 (6%)	Yes: 12 (4%) **No: 280 (93%)** I don't know: 9 (3%)	Yes: 7 (2%) **No: 300 (94%)** I don't know: 11 (4%)
Dental pain	Yes: 6 (89%)	Yes: 3 (1%)	Yes: 5 (2%)	Yes: 2 (1%)	Yes: 2 (1%)

	No: 286 (95%) I don't know: 10 (3%)	**No: 290 (97%)** I don't know: 7 (2%)	**No: 291 (97%)** I don't know: 4 (1%)	**No: 296 (98%)** I don't know: 3 (1%)	**No: 306 (96%)** I don't know: 10 (3%)
Breakthrough pain from cancer	**Yes: 252 (83%)** No: 46 (15%) I don't know: 4 (1%)	**Yes: 268 (89%)** No: 27 (9%) I don't know: 5 (2%)	**Yes: 275 (92%)** No: 23 (8%) I don't know: 2 (1%)	**Yes: 277 (92%)** No: 24 (8%) I don't know: 0 (0%)	**Yes: 292 (92%)** No: 22 (7%) I don't know: 4 (1%)
Chronic non-cancer pain	Yes: 194 (64%) **No: 90 (30%)** I don't know: 18 (6%)	Yes: 126 (42%) **No: 141 (47%)** I don't know: 33 (11%)	Yes: 146 (49%) **No: 131 (44%)** I don't know: 23 (8%)	Yes: 131 (44%) **No: 153 (51%)** I don't know: 17 (6%)	Yes: 138 (43%) **No: 162 (51%)** I don't know: 18 (6%)
Composite Score	**61%***	**40%**	**37%**	**22%**	**22%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

Table 10.6.3.: Pharmacists' Understanding of Key Risk Message 3

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=300**	**36 Month Survey** **N=300**	**48 Month Survey** **N=301**	**60 Month Survey** **N=318**
It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**True: 295 (98%)** False: 5 (2%) I don't know: 2 (1%)	**True: 290 (97%)** False: 5 (2%) I don't know: 5 (2%)	**True: 288 (96%)** False: 7 (2%) I don't know: 5 (2%)	**True: 293 (97%)** False: 7 (2%) I don't know: 1 (<1%)	**True: 312 (98%)** False: 4 (1%) I don't know: 2 (1%)
Which of the following are risk factors for opioid abuse?					
A personal history of psychiatric illness	**Yes: 201 (67%)** No: 62 (20.5%) I don't know: 39 (13%)	**Yes: 216 (72%)** No: 48 (16%) I don't know: 36 (12%)	**Yes: 213 (71%)** No: 46 (15%) I don't know: 41 (14%)	**Yes: 227 (75%)** No: 43 (14%) I don't know: 31 (10%)	**Yes: 247 (78%)** No: 42 (13%) I don't know: 29 (9%)

A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**Yes: 301 (100%)** No: 0 (15%) I don't know: 1 (0.3%)	**Yes: 297 (99%)** No: 0 (0%) I don't know: 3 (1%)	**Yes: 298 (99%)** No: 0 (0%) I don't know: 2 (1%)	**Yes: 297 (99%)** No: 2 (1%) I don't know: 2 (1%)	**Yes: 314 (99%)** No: 1 (<1%) I don't know: 3 (1%)
TIRF medicines can be abused in a manner similar to other opioid agonist.	**True: 273 (90%)** False: 19 (6%) I don't know: 10 (3%)	**True: 282 (94%)** False: 10 (3%) I don't know: 8 (3%)	**True: 283 (94%)** False: 12 (4%) I don't know: 5 (2%)	**True: 288 (96%)** False: 8 (3%) I don't know: 5 (2%)	**True: 298 (94%)** False: 12 (4%) I don't know: 8 (3%)
Which of the following risks are associated with the use of TIRF medicines?					
Misuse	N/A	N/A	N/A	N/A	**True: 314 (99%)** False: 3 (1%) I don't know: 1 (<1%)
Abuse	N/A	N/A	N/A	N/A	**True: 315 (99%)** False: 2 (1%) I don't know: 1 (<1%)
Addiction	N/A	N/A	N/A	N/A	**True: 314 (99%)** False: 3 (1%) I don't know: 1 (<1%)
Overdose	N/A	N/A	N/A	N/A	**True: 316 (99%)** False: 1 (<1%) I don't know: 1 (<1%)
Composite Score	**60%**	**66%**	**66%**	**69%**	**59%***

* Questions added to the 60 month assessment Key Risk Message that were not included for the previous months

Table 10.6.4.: Pharmacists' Understanding of Key Risk Message 4

Question	12 Month Survey N=302	24 Month Survey N=300	36 Month Survey N=300	48 Month Survey N=301	60 Month Survey N=318
TIRF medicines are interchangeable with each other regardless of route of administration	True: 9 (3%) **False: 287 (95%)** I don't know: 6 (2%)	True: 6 (2%) **False: 284 (95%)** I don't know: 10 (3%)	True: 13 (4%) **False: 280 (93%)** I don't know: 7 (2%)	True: 14 (5%) **False: 281 (93%)** I don't know: 6 (2%)	True: 6 (2%) **False: 305 (96%)** I don't know: 7 (2%)
The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of the differences in the pharmacokinetics of fentanyl absorption.	**True: 280 (93%)** False: 10 (3%) I don't know: 12 (4%)	**True: 276 (92%)** False: 5 (2%) I don't know: 19 (6%)	**True: 279 (93%)** False: 13 (4%) I don't know: 8 (3%)	**True: 279 (93%)** False: 11 (4%) I don't know: 11 (4%)	**True: 296 (93%)** False: 10 (3%) I don't know: 12 (4%)
Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**True: 279 (92%)** False: 10 (3%) I don't know: 13 (4%)	**True: 274 (91%)** False: 10 (3%) I don't know: 16 (5%)	**True: 270 (90%)** False: 20 (7%) I don't know: 10 (3%)	**True: 279 (93%)** False: 14 (5%) I don't know: 8 (3%)	**True: 283 (89%)** False: 16 (5%) I don't know: 19 (6%)
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: 5 (2%) **False: 289 (96%)** I don't know: 8 (3%)	True: 6 (2%) **False: 289 (96%)** I don't know: 5 (2%)	True: 2 (1%) **False: 293 (98%)** I don't know: 5 (2%)	True: 3 (1%) **False: 296 (98%)** I don't know: 2 (1%)	True: 10 (3%) **False: 304 (96%)** I don't know: 4 (1%)
Composite Score	**84%**	**85%**	**81%**	**81%**	**80%**

Table 10.6.5.: Pharmacists' Understanding of Safe Use Questions

Question	12 Month Survey N=302	24 Month Survey N=300	36 Month Survey N=300	48 Month Survey N=301	60 Month Survey N=318
Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.	**N/A**	N/A	N/A	**True: 275 (91%)** False: 8 (3%) I don't know: 18 (6%)	**True: 293 (92%)** False: 3 (1%) I don't know: 22 (7%)
TIRF medicines may be sold, loaned, or transferred to another pharmacy.	True: 14 (5%) **False: 262 (87%)** I don't know: 26 (9%)	True: 8 (3%) **False: 274 (91%)** I don't know: 18 (6%)	True: 11 (4%) **False: 276 (92%)** I don't know: 13 (4%)	True: 7 (2%) **False: 279 (93%)** I don't know: 15 (5%)	True: 16 (5%) **False: 288 (91%)** I don't know: 14 (4%)
All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.	**True: 280 (93%)** False: 12 (4%) I don't know: 10 (3%)	**True: 282 (94%)** False: 6 (2%) I don't know: 12 (4%)	**True: 284 (95%)** False: 10 (3%) I don't know: 6 (2%)	**True: 273 (91%)** False: 23 (8%) I don't know: 5 (2%)	**True: 286 (90%)** False: 18 (6%) I don't know: 14 (4%)
It is ok to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	True: 2 (12.5%) **False: 14 (87.5%)** I don't know: 0 (0%)	True: 0 (0%) **False: 13 (87%)** I don't know: 2 (13%)	True: 2 (13%) **False: 13 (87%)** I don't know: 0 (0%)	True: 0 (0%) **False: 13 (87%)** I don't know: 2 (13%)	True: 3 (5%) **False: 54 (83%)** I don't know: 8 (12%)

*Inpatient pharmacists only (12 month: n=16; 24 month: n=15; 36 month: n=15; 48 month: n=15); 60 month: n=65					

Table 10.6.6.: Pharmacists' Reported Activities When Dispensing TIRF Medicines

Question	**12 Month Survey N=302**	**24 Month Survey N=300**	**36 Month Survey N=300**	**48 Month Survey N=301**	**60 Month Survey N=318**
How frequently do you perform the following activities when dispensing TIRF medicines?					
Ask patients about the presence of children in the home.	Always: 146 (48%) Only with the first prescription: 68 (22.5%) Sometimes: 54 (18%) Never: 28 (9%) I don't know: 6 (2%)	Always: 167 (56%) Only with the first prescription: 54 (18%) Sometimes: 54 (18%) Never: 13 (4%) I don't know: 12 (4%)	Always: 174 (58%) Only with the first prescription: 68 (23%) Sometimes: 33 (11%) Never: 14 (5%) I don't know: 11 (4%)	Always: 180 (60%) Only with the first prescription: 67 (22%) Sometimes: 36 (12%) Never: 9 (3%) I don't know: 9 (3%)	Always: 180 (60%) Only with the first prescription: 67 (22%) Sometimes: 36 (12%) Never: 9 (3%) I don't know: 9 (3%)
Instruct patients not to share the TIRF medicines with anyone else.	Always: 202 (67%) Only with the first prescription: 54 (18%) Sometimes: 26 (9%) Never: 15 (5%)	Always: 208 (69%) Only with the first prescription: 52 (17%) Sometimes: 26 (9%) Never: 8 (3%)	Always: 224 (75%) Only with the first prescription: 45 (15%) Sometimes: 17 (6%) Never: 6 (2%)	Always: 235 (78%) Only with the first prescription: 42 (14%) Sometimes: 14 (5%) Never: 6 (2%)	Always: 235 (78%) Only with the first prescription: 42 (14%) Sometimes: 14 (5%) Never: 6 (2%)

	I don't know: 5 (2%)	I don't know: 6 (2%)	I don't know: 8 (3%)	I don't know: 4 (1%)	I don't know: 4 (1%)
Counsel patients that accidental exposure to TIRF medicines by a child may be fatal	Always: 190 (63%) Only with the first prescription: 63 (21%) Sometimes: 29 (10%) Never: 13 (4%) I don't know: 7 (2%)	Always: 198 (66%) Only with the first prescription: 57 (19%) Sometimes: 29 (10%) Never: 8 (3%) I don't know: 8 (3%)	Always: 216 (72%) Only with the first prescription: 53 (18%) Sometimes: 16 (5%) Never: 6 (2%) I don't know: 9 (3%)	Always: 216 (72%) Only with the first prescription: 48 (16%) Sometimes: 27 (9%) Never: 4 (1%) I don't know: 6 (2%)	Always: 216 (72%) Only with the first prescription: 48 (16%) Sometimes: 27 (9%) Never: 4 (1%) I don't know: 6 (2%)
Instruct patients to keep TIRF medicines out of reach of children to prevent accidental exposure.	Always: 208 (69%) Only with the first prescription: 56 (18.5%) Sometimes: 21 (7%) Never: 12 (4%) I don't know: 5 (2%)	Always: 223 (74%) Only with the first prescription: 44 (15%) Sometimes: 23 (8%) Never: 4 (1%) I don't know: 5 (2%)	Always: 224 (75%) Only with the first prescription: 48 (16%) Sometimes: 17 (6%) Never: 3 (1%) I don't know: 8 (3%)	Always: 238 (79%) Only with the first prescription: 39 (13%) Sometimes: 16 (5%) Never: 4 (1%) I don't know: 4 (1%)	Always: 238 (79%) Only with the first prescription: 39 (13%) Sometimes: 16 (5%) Never: 4 (1%) I don't know: 4 (1%)
Instruct patients about proper disposal of any unused or partially used TIRF medicines.	Always: 172 (57%) Only with the first prescription: 76 (25%) Sometimes: 34 (11%) Never: 13 (4%) I don't know: 7 (2%)	Always: 198 (66%) Only with the first prescription: 67 (22%) Sometimes: 26 (9%) Never: 4 (1%) I don't know: 5 (2%)	Always: 203 (68%) Only with the first prescription: 63 (21%) Sometimes: 23 (8%) Never: 2 (1%) I don't know: 8 (3%)	Always: 209 (69%) Only with the first prescription: 66 (22%) Sometimes: 20 (7%) Never: 3 (1%) I don't know: 3 (1%)	Always: 209 (69%) Only with the first prescription: 66 (22%) Sometimes: 20 (7%) Never: 3 (1%) I don't know: 3 (1%)
Give patients the Medication Guide for their TIRF medicine.	Always: 272 (90%) Only with the first prescription: 17 (6%) Sometimes: 5 (2%)	Always: 274 (91%) Only with the first prescription: 11 (4%) Sometimes: 10 (3%)	Always: 268 (89%) Only with the first prescription: 20 (7%) Sometimes: 3 (1%)	Always: 278 (92%) Only with the first prescription: 14 (5%) Sometimes: 4 (1%)	Always: 278 (92%) Only with the first prescription: 14 (5%) Sometimes: 4 (1%)

	Never: 3 (1%) I don't know: 5 (2%)	Never: 0 (0%) I don't know: 5 (2%)	Never: 1 (0.3%) I don't know: 8 (3%)	Never: 2 (1%) I don't know: 3 (1%)	Never: 2 (1%) I don't know: 3 (1%)
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 (12 month: n=16; 24 month: n=15; 36 month: n=15; 48 month: n=15)	Yes: 8 (50%) No: 6 (37.5%) I don't know: 2 (12.5%)	Yes: 8 (53%) No: 4 (27%) I don't know: 3 (20%)	Yes: 7 (48%) No: 5 (33%) I don't know: 3 (20%)	Yes: 8 (53%) No: 7 (47%) I don't know: 0 (0%)	Yes: 8 (53%) No: 7 (47%) I don't know: 0 (0%)
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 pharmacist only (12 month: n=280;	Yes: 235 (84%) No: 7 (2.5%) I don't know: 38 (14%)	Yes: 231 (82%) No: 5 (2%) I don't know: 45 (16%)	Yes: 254 (89%) No: 6 (2%) I don't know: 24 (8.5%)	Yes: 262 (92%) No: 10 (4%) I don't know: 14 (5%)	Yes: 262 (92%) No: 10 (4%) I don't know: 14 (5%)

24 month: 281; 36 month: n=284; 48 month: n=289)					
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 (12 month: n=6; 24 month: n=2; 36 month: n=1)	Yes: 5 (83%) No: 0 (0%) I don't know: 1 (17%)	Yes: 2 (50%) No: 0 (0%) I don't know: 2 (50%)	Yes: 1 (100%) No: 0 (0%) I don't know: 0 (0%)	N/A	N/A

10.7. Prescriber Survey Tables

Table 10.7.1: Prescribers' Understanding of Key Risk Message 1

Question	12 Month Survey N=302	24 Month Survey N=302	36 Month Survey N=300	48 Month Survey N=310	60 Month Survey N=294
TIRF medicines should only be taken by patients who are opioid tolerant.					**True: 284 (97%)** False: 8 (3%) I don't know: 2 (1%)
24, 48, 60 month: According to labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: 12 month: According to the labeling, patients considered opioid-tolerant are those:					
Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (**T**/F/DK)	**True: 24 (8%)** False: 271 (89%) I don't know: 7 (2%)	**True: 273 (90%)** False: 24 (8%) I don't know: 5 (2%)	**True: 270 (90%)** False: 22 (7%) I don't know: 8 (3%)	**True: 295 (95%)** False: 14 (5%) I don't know: 1 (<1%)	**True: 279 (95%)** False: 11 (4%) I don't know: 4 (1%)
Who are not currently taking opioid therapy, but have taken opioid therapy before.	True: 25 (8%) **False: 268 (89%)** I don't know: 9 (3%)	True: 28 (9%) **False: 266 (88%)** I don't know: 8 (3%)	True: 24 (8%) **False: 261 (87%)** I don't know: 15 (5%)	True: 15 (5%) **False: 291 (94%)** I don't know: 4 (1%)	True: 65 (5%) **False: 276 (94%)** I don't know: 2 (1%)
Who have no known contraindications to the drug fentanyl, but are not currently taking around-the clock opioid therapy 12 month: Who are not currently taking opioid therapy, but with no known	True: 251 (83%) **False: 47 (16%)** I don't know: 4 (1%)	True: 39 (13%) **False: 248 (82%)** I don't know: 15 (5%)	True: 28 (9%) **False: 259 (86%)** I don't know: 13 (4%)	True: 33 (11%) **False: 269 (87%)** I don't know: 8 (3%)	True: 17 (6%) **False: 272 (93%)** I don't know: 5 (2%)

intolerance or hypersensitivity to the drug fentanyl					
TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**True: 264 (87%)** False: 35 (12%) I don't know: 3 (1%)	**True: 265 (88%)** False: 32 (11%) I don't know: 5 (2%)	**True: 260 (87%)** False: 32 (11%) I don't know: 8 (3%)	**True: 280 (90%)** False: 23 (7%) I don't know: 7 (2%)	**True: 270 (92%)** False: 21 (7%) I don't know: 3 (1%)
Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**True: 289 (96%)** False: 4 (1%) I don't know: 9 (3%)	**True: 283 (94%)** False: 3 (1%) I don't know: 16 (5%)	**True: 287 (96%)** False: 2 (1%) I don't know: 11 (4%)	**True: 298 (96%)** False: 2 (1%) I don't know: 10 (3%)	**True: 281 (96%)** False: 3 (1%) I don't know: 10 (3%)
TIRF medicines may be used in opioid non-tolerant patients.	True: 45 (15%) **False: 249 (82.5%)** I don't know: 8 (3%)	True: 43 (14%) **False: 242 (80%)** I don't know: 17 (6%)	True: 46 (15%) **False: 246 (82%)** I don't know: 8 (3%)	True: 38 (12%) **False: 263 (85%)** I don't know: 9 (3%)	True: 27 (9%) **False: 260 (88%)** I don't know: 7 (2%)
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: 251 (83%)** False: 45 (15%) I don't know: 6 (2%)	**True: 244 (81%)** False: 52 (17%) I don't know: 6 (2%)	**True: 252 (84%)** False: 42 (14%) I don't know: 6 (2%)	**True: 265 (86%)** False: 40 (13%) I don't know: 5 (2%)	**True: 252 (86%)** False: 37 (13%) I don't know: 5 (2%)
According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:					
8 mg oral hydromorphone/day	**N/A**	**True: 207 (68.5%)** False: 64 (21%) I don't know: 31 (10%)	**True: 211 (70%)** False: 66 (22%) I don't know: 23 (8%)	**True: 226 (73%)** False: 57 (18%) I don't know: 27 (9%)	**True: 211 (72%)** False: 69 (24%) I don't know: 14 (5%)

60 mg oral morphine/day	**N/A**	**True: 269 (89%)** False: 16 (5%) I don't know: 17 (6%)	**True: 277 (92%)** False: 42 (14%) I don't know: 12 (4%)	**True: 293 (95%)** False: 57 (18%) I don't know: 27 (9%)	**True: 281 (96%)** False: 6 (2%) I don't know: 7 (2%)
30 mg oral oxycodone/day	**N/A**	**True: 230 (76%)** False: 47 (16%) I don't know: 25 (8%)	**True: 234 (78%)** False: 42 (14%) I don't know: 24 (8%)	**True: 244 (79%)** False: 46 (15%) I don't know: 20 (7%)	**True: 241 (82%)** False: 44 (15%) I don't know: 9 (3%)
25 mcg transdermal fentanyl/hour	**N/A**	**True: 244 (81%)** False: 34 (11%) I don't know: 24 (8%)	**True: 251 (84%)** False: 31 (10%) I don't know: 18 (6%)	**True: 265 (86%)** False: 27 (9%) I don't know: 18 (6%)	**True: 262 (89%)** False: 21 (7%) I don't know: 11 (4%)
25 mg oral oxymorphone/day	**N/A**	**True: 211 (70%)** False: 39 (13%) I don't know: 52 (17%)	**True: 224 (75%)** False: 41 (14%) I don't know: 34 (12%)	**True: 224 (72%)** False: 33 (11%) I don't know: 53 (17%)	**True: 234 (80%)** False: 33 (11%) I don't know: 27 (9%)
An equianalgesic dose of another oral opioid	**N/A**	**True: 199 (66%)** False: 68 (22.5%) I don't know: 35 (12%)	**True: 177 (59%)** False: 66 (22%) I don't know: 57 (19%)	**True: 210 (68%)** False: 55 (18%) I don't know: 45 (15%)	**True: 193 (66%)** False: 56 (19%) I don't know: 45 (15%)
Composite Score	**65%***	**45%**	**50%**	**30%**	**33%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

Table 10.7.2.: Prescribers' Understanding of Key Risk Message 2

Question	**12 Month Survey**	**24 Month Survey**	**36 Month Survey**	**48 Month Survey**	**60 Month Survey**

	N=302	**N=302**	**N=300**	**N=310**	**N=294**
A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	**N/A**	True: 105 (35%) **False: 183 (61%)** I don't know: 14 (5%)	True: 101 (34%) **False: 180 (60%)** I don't know: 19 (6%)	True: 75 (24%) **False: 214 (69%)** I don't know: 21 (7%)	True: 52 (18%) **False: 227 (77%)** I don't know: 15 (5%)
A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	**N/A**	True: 86 (28.5%) **False: 196 (65%)** I don't know: 20 (7%)	True: 68 (23%) **False: 211 (70%)** I don't know: 21 (7%)	True: 62 (20%) **False: 226 (73%)** I don't know: 22 (7%)	True: 54 (18%) **False: 230 (78%)** I don't know: 10 (3%)
Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?					
Acute or postoperative pain	Yes: 38 (13%) **No: 261 (86%)** I don't know: 3 (1%)	Yes: 17 (6%) **No: 281 (93%)** I don't know: 4 (1%)	Yes: 37 (12%) **No: 262 (87%)** I don't know: 1 (0.3%)	Yes: 28 (9%) **No: 280 (90%)** I don't know: 2 (1%)	Yes: 9 (3%) **No: 278 (95%)** I don't know: 7 (2%)
Headache or migraine pain	Yes: 38 (13%) **No: 262 (87%)** I don't know: 2 (1%)	Yes: 20 (7%) **No: 279 (92%)** I don't know: 3 (1%)	Yes: 31 (10%) **No: 269 (90%)** I don't know: 0 (0%)	Yes: 16 (5%) **No: 294 (95%)** I don't know: 0 (0%)	Yes: 6 (2%) **No: 276 (94%)** I don't know: 12 (4%)
Dental pain	Yes: 7 (2%) **No: 290 (96%)** I don't know: 5 (2%)	Yes: 5 (2%) **No: 292 (97%)** I don't know: 5 (2%)	Yes: 8 (3%) **No: 292 (97%)** I don't know: 0 (0%)	Yes: 5 (2%) **No: 305 (98%)** I don't know: 0 (0%)	Yes: 4 (1%) **No: 283 (96%)** I don't know: 7 (2%)
Breakthrough pain from cancer	**Yes: 288 (95%)** No: 14 (5%) I don't know: 0 (0%)	**Yes: 279 (92%)** No: 22 (7%) I don't know: 1 (0.3%)	**Yes: 288 (96%)** No: 12 (4%) I don't know: 0 (0%)	**Yes: 288 (93%)** No: 22 (7%) I don't know: 0 (0%)	**Yes: 292 (99%)** No: 2 (1%) I don't know: 0 (0%)

Chronic non-cancer pain	Yes: 134 (44%) **No: 164 (54%)** I don't know: 4 (1%)	Yes: 119 (39%) **No: 178 (59%)** I don't know: 5 (2%)	Yes: 112 (37%) **No: 186 (62%)** I don't know: 2 (1%)	Yes: 106 (34%) **No: 201 (65%)** I don't know: 3 (1%)	Yes: 54 (18%) **No: 230 (78%)** I don't know: 10 (3%)
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	**164 (54%)**	**199 (66%)**	**199 (66%)**	**227 (73%)**	**212 (72%)**
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: 277 (92%)** False: 16 (5%) I don't know: 9 (3%)	**True: 278 (92%)** False: 16 (5%) I don't know: 8 (3%)	**True: 272 (91%)** False: 16 (5%) I don't know: 12 (4%)	**True: 291 (94%)** False: 12 (4%) I don't know: 7 (2%)	**True: 283 (96%)** False: 8 (3%) I don't know: 3 (1%)
Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.	True: 63 (21%) **False: 207 (68.5%)** I don't know: 32 (11%)	True: 95 (31.5%) **False: 175 (58%)** I don't know: 32 (11%)	True: 89 (30%) **False: 183 (61%)** I don't know: 28 (9%)	True: 64 (21%) **False: 226 (73%)** I don't know: 20 (7%)	True: 58 (20%) **False: 225 (77%)** I don't know: 11 (4%)
Composite Score	**61%***	**39%**	**36%**	**33%**	**33%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

Table 10.7.3.: Prescribers' Understanding of Key Risk Message 3

Question	12 Month Survey N=302	24 Month Survey N=302	36 Month Survey N=300	48 Month Survey N=310	60 Month Survey N=294
It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**True: 301 (100%)** False: 1 (0.3%) I don't know: 0 (0%)	**True: 299 (99%)** False: 2 (1%) I don't know: 1 (0.3%)	**True: 299 (100%)** False: 1 (0.3%) I don't know: 0 (0%)	**True: 306 (99%)** False: 2 (1%) I don't know: 2 (1%)	**True: 291 (99%)** False: 3 (1%) I don't know: 0 (0%)
Which of the following are risk factors for opioid abuse?					
A personal history of psychiatric illness	**Yes: 249 (82.5%)** No: 37 (12%) I don't know: 16 (5%)	**Yes: 250 (83%)** No: 31 (10%) I don't know: 21(7%)	**Yes: 252 (84%)** No: 23 (8%) I don't know: 25 (8%)	**Yes: 262 (85%)** No: 28 (9%) I don't know: 20 (7%)	**Yes: 253 (86%)** No: 27 (9%) I don't know: 14 (5%)
A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**Yes: 300 (99%)** No: 1 (0.3%) I don't know: 1 (0.3%)	**Yes: 299 (99%)** False: 2 (1%) I don't know: 1 (0.3%)	**Yes: 299 (100%)** No: 1 (0.3%) I don't know: 0 (0%)	**Yes: 306 (99%)** No: 4 (1%) I don't know: 0 (0%)	**Yes: 294 (100%)** No: 0 (0%) I don't know: 0 (0%)
TIRF medicines can be abused in a manner similar to other opioid agonist.	**True: 295 (98%)** False: 6 (2%) I don't know: 1 (0.3%)	**True: 291 (96%)** False: 9 (3%) I don't know: 2 (1%)	**True: 292 (97%)** False: 7 (2%) I don't know: 1 (0.3%)	**True: 292 (94%)** False: 12 (4%) I don't know: 6 (2%)	**True: 282 (96%)** False: 10 (3%) I don't know: 2 (1%)
Which of the following risks are associated with the use of TIRF medicines?					
Misuse	N/A	N/A	N/A	N/A	**True: 290 (99%)**

					False: 4 (1%) I don't know: 0 (0%)
Abuse	N/A	N/A	N/A	N/A	**True: 291 (99%)** False: 2 (1%) I don't know: 1 (<1%)
Addiction	N/A	N/A	N/A	N/A	**True: 291 (99%)** False: 3 (1%) I don't know: 0 (0%)
Overdose	N/A	N/A	N/A	N/A	**True: 292 (99%)** False: 2 (1%) I don't know: 0 (0%)
Composite Score	**80%**	**80%**	**82%**	**79%**	**61%***

*Questions added for 60-month assessment

Table 10.7.4.: Prescribers' Understanding of Key Risk Message 4

Question	**12 Month Survey N=302**	**24 Month Survey N=302**	**36 Month Survey N=300**	**48 Month Survey N=310**	**60 Month Survey N=294**
TIRF medicines are interchangeable with each other regardless of route of administration	True: 9 (3%) **False: 289 (96%)** I don't know: 4 (1%)	True: 16 (5%) **False: 279 (92%)** I don't know: 7 (2%)	True: 15 (5%) **False: 279 (93%)** I don't know: 6 (2%)	True: 13 (4%) **False: 287 (93%)** I don't know: 10 (3%)	True: 15 (5%) **False: 271 (92%)** I don't know: 8 (3%)
The conversion of one TIRF medicine for another TIRF medicine	**True: 286 (95%)** False: 5 (2%)	**True: 286 (95%)** False: 7 (2%)	**True: 290 (97%)** False: 6 (2%)	**True: 296 (96%)** False: 6 (2%)	**True: 283 (96%)** False: 5 (2%)

may result in a fatal overdose because of the differences in the pharmacokinetics of fentanyl absorption.	I don't know: 11 (4%)	I don't know: 9 (3%)	I don't know: 4 (1%)	I don't know: 8 (3%)	I don't know: 6 (2%)
Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**True: 273 (90%)** False: 12 (4%) I don't know: 17 (6%)	**True: 274 (91%)** False: 16 (5%) I don't know: 12 (4%)	**True: 272 (91%)** False: 18 (6%) I don't know: 10 (3%)	**True: 279 (90%)** False: 21 (7%) I don't know: 10 (3%)	**True: 269 (92%)** False: 11 (4%) I don't know: 14 (5%)
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. His/her doctor decides to prescribe a different TIRF medicine in its place. According to the labeling, how should the prescriber proceed?					
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.	**228 (75.5%)**	**225 (74.5%)**	**223 (74%)**	**240 (77%)**	**231 (79%)**
Composite Score	**85%***	**65%**	**67%**	**67%**	**70%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

Table 10.7.5.: Prescribers' Understanding of Safe Use Questions

Question	**12 Month Survey N=302**	**24 Month Survey N=302**	**36 Month Survey N=300**	**48 Month Survey N=310**	**60 Month Survey N=294**

A patient is starting titration with TIRF medicine. What dose must they start with? The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.	**276 (91%)**	**252 (84%)**	**267 (89%)**	**267 (86%)**	**266 (91%)**
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? Provide guidance based on the product-specific MG because the instructions are not the same for all TIRF medicines.	**273 (90%)**	**205 (68%)**	**199 (66%)**	**213 (69%)**	**208 (71%)**
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.	**262 (87%)**	**225 (74.5%)**	**232 (77%)**	**235 (76%)**	**235 (80%)**

Use of a TIRF medicine with a CYP2A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.					
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: 299 (99%)** False: 1 (0.3%) I don't know: 2 (1%)	**True: 298 (99%)** False: 1 (0.3%) I don't know: 3 (1%)	**True: 298 (99%)** False: 0 (0%) I don't know: 2 (1%)	**True: 308 (99%)** False: 1 (<1%) I don't know: 1 (<1%)	**True: 293 (99.7%)** False: 0 (0%) I don't know: 1 (<1%)
Instruct patients never to share their TIRF medicines with anyone else, even if that person has the same symptoms.	**True: 300 (99%)** False: 1 (0.3%) I don't know: 1 (0.3%)	**True: 299 (99%)** False: 3 (1%) I don't know: 0 (0%)	**True: 297 (99%)** False: 2 (1%) I don't know: 1 (0.3%)	**True: 309 (99.7%)** False: 0 (0%) I don't know: 1 (<1%)	**True: 294 (100%)** False: 0 (0%) I don't know: 0 (0%)

Table 10.7.6.: Prescribers' Reported Activities When Dispensing TIRF Medicines

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=302**	**36 Month Survey** **N=300**	**48 Month Survey** **N=310**	**60 Month Survey** **N=294**
How frequently do you perform the following activities when dispensing TIRF medicines?					

Ask patients about the presence of children in the home.	Always: 175 (58%) Only with the first prescription: 76 (25%) Sometimes: 44 (15%) Never: 5 (2%) I don't know: 2 (1%)	Always: 170 (56%) Only with the first prescription: 70 (23%) Sometimes: 48 (16%) Never: 11 (4%) I don't know: 3 (1%)	Always: 169 (56%) Only with the first prescription: 81 (27%) Sometimes: 42 (14%) Never: 7 (2%) I don't know: 1 (0.3%)	Always: 178 (57%) Only with the first prescription: 75 (24%) Sometimes: 42 (14%) Never: 11 (4%) I don't know: 4 (1%)	Always: 182 (62%) Only with the first prescription: 66 (22%) Sometimes: 35 (12%) Never: 10 (3%) I don't know: 1 (<1%)
Instruct patients not to share the TIRF medicines with anyone else.	Always: 239 (79%) Only with the first prescription: 36 (12%) Sometimes: 24 (8%) Never: 1 (0.3%) I don't know: 2 (1%)	Always: 239 (79%) Only with the first prescription: 37 (12%) Sometimes: 19 (6%) Never: 5 (2%) I don't know: 2 (1%)	Always: 235 (78%) Only with the first prescription: 41 (14%) Sometimes: 17 (6%) Never: 6 (2%) I don't know: 1 (0.3%)	Always: 249 (80%) Only with the first prescription: 43 (14%) Sometimes: 13 (4%) Never: 3 (1%) I don't know: 2 (1%)	Always: 236 (80%) Only with the first prescription: 43 (15%) Sometimes: 14 (5%) Never: 1 (<1%) I don't know: 0 (0%)
Counsel patients that accidental exposure to TIRF medicines by a child may be fatal	Always: 199 (66%) Only with the first prescription: 59 (19.5%) Sometimes: 24 (8%) Never: 1 (0.3%) I don't know: 2 (1%)	Always: 197 (65%) Only with the first prescription: 63 (21%) Sometimes: 31 (10%) Never: 8 (3%) I don't know: 3 (1%)	Always: 204 (68%) Only with the first prescription: 66 (22%) Sometimes: 26 (9%) Never: 3 (1%) I don't know: 1 (0.3%)	Always: 203 (66%) Only with the first prescription: 66 (21%) Sometimes: 27 (9%) Never: 11 (4%) I don't know: 3 (1%)	Always: 208 (71%) Only with the first prescription: 55 (19%) Sometimes: 23 (8%) Never: 8 (3%) I don't know: 0 (0%)
Instruct patients to keep TIRF medicines out of reach of children to prevent accidental exposure.	Always: 220 (73%) Only with the first prescription: 51 (17%) Sometimes: 25 (8%) Never: 4 (1%)	Always: 220 (73%) Only with the first prescription: 46 (15%) Sometimes: 28 (9%) Never: 5 (2%)	Always: 223 (74%) Only with the first prescription: 52 (17%) Sometimes: 22 (7%) Never: 2 (1%)	Always: 220 (71%) Only with the first prescription: 61 (20%) Sometimes: 19 (6%) Never: 7 (2%)	Always: 232 (79%) Only with the first prescription: 44 (15%) Sometimes: 13 (4%) Never: 5 (2%)

	I don't know: 2 (1%)	I don't know: 3 (1%)	I don't know: 1 (0.3%)	I don't know: 3 (1%)	I don't know: 0 (0%)
Instruct patients about proper disposal of any unused or partially used TIRF medicines.	Always: 184 (61%) Only with the first prescription: 75 (25%) Sometimes: 37 (12%) Never: 4 (1%) I don't know: 2 (1%)	Always: 187 (62%) Only with the first prescription: 62 (20.5%) Sometimes: 37 (12%) Never: 12 (4%) I don't know: 4 (1%)	Always: 186 (62%) Only with the first prescription: 68 (23%) Sometimes: 38 (13%) Never: 7 (2%) I don't know: 1 (0.3%)	Always: 190 (61%) Only with the first prescription: 74 (24%) Sometimes: 37 (12%) Never: 6 (2%) I don't know: 3 (1%)	Always: 197 (67%) Only with the first prescription: 56 (19%) Sometimes: 34 (12%) Never: 7 (2%) I don't know: 0 (0%)
Give patients the Medication Guide for their TIRF medicine.	Always: 122 (40%) Only with the first prescription: 128 (42%) Sometimes: 28 (9%) Never: 20 (7%) I don't know: 4 (1%)	Always: 142 (47%) Only with the first prescription: 108 (36%) Sometimes: 26 (9%) Never: 20 (7%) I don't know: 6 (2%)	Always: 127 (42%) Only with the first prescription: 124 (41%) Sometimes: 35 (12%) Never: 11 (4%) I don't know: 3 (1%)	Always: 140 (45%) Only with the first prescription: 123 (40%) Sometimes: 23 (7%) Never: 21 (7%) I don't know: 3 (1%)	Always: 130 (44%) Only with the first prescription: 131 (45%) Sometimes: 17 (6%) Never: 15 (5%) I don't know: 1 (<1%)
Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	N/A	N/A	N/A	N/A	Always: 223 (76%) Only with the first prescription: 53 (18%) Sometimes: 16 (5%) Never: 0 (0%) I don't know: 2 (1%)
Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	N/A	N/A	N/A	N/A	Always: 204 (69%) Only with the first prescription: 67 (23%) Sometimes: 21 (7%)

					Never: 0 (0%) I don't know: 2 (1%)
Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	N/A	N/A	N/A	N/A	Always: 156 (53%) Only with the first prescription: 102 (35%) Sometimes: 22 (8%) Never: 12 (4%) I don't know: 2 (1%)

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/s/

IGOR CERNY
12/05/2017
REMS Assessment Review

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12/05/2017

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