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January 30, 2017

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

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Correspondence
eCTD Sequence Number: 0026

Dear Drug Master File Staff:

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

Please find the consolidated response document to the multiple FDA information requests regarding the TIRF REMS Access Program 48-Month FDA Assessment Report located in Module 1.6 of this submission. Please see Page 1 of the consolidated response document for a summary of the FDA requests and correspondences.

In addition, the Transmucosal REMS Industry Group (TRIG) would like to confirm receipt of the FDA Information Request as a follow-up to the 48-month Acknowledgement Letter. The request is currently in process and the TRIG acknowledges that each individual sponsor will be submitting a separate supplemental correspondence through their individual application to FDA prior to March 30, 2017.

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

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

If you have any questions or concerns, please do not hesitate to contact Debra Hackett, U.S. Agent for McKesson, at 610-407-1729 or alternatively via email at debra.hackett@accenture.com.

DMF #: 027320; Sequence 0026
Shared System REMS

Sincerely,

Debra Hackett, U.S. Agent
Accenture, LLP

Attachments: Table of Contents for the submission
Electronic Submission Specifications

REMS CORRESPONDENCE

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments
1.16 – Risk Management Plans	REMS History TIRF REMS Access Program 48-Month FDA Assessment Report Consolidated Information Request DMF Submission

Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	12.1.5337.5000
Virus Definition Date	01/26/2017 rev. 8
Submission Size	Approx. 3.9 MB

The IT point of contact for this submission is:

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ADMINISTRATIVE INFORMATION

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Statement of Commitment: Attached, please find a signed statement of commitment. The statement certifies that the DMF 027320 is current and that McKesson will comply with the statements made in it.

Agent's Name: Accenture, LLP

Agent's Address: 1160 West Swedesford Road, Building One
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Agent's Contact Person: Debra Hackett, Senior Regulatory Project Manager, Regulatory Affairs

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Contact's Fax: 610-407-8433

Contact's E-mail address: debra.hackett@accenture.com

Modification No.	Date Approved	Documents Affected	Overview of Modification
1	June 5, 2012	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient Provider Agreement Form • Patient and Caregiver Overview • Dear Healthcare Provider Letter • Outpatient Pharmacy Overview • Chain Pharmacy Overview • Inpatient Pharmacy Overview • Outpatient Pharmacy Enrollment Form • Chain Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Outpatient Pharmacy Letter • Inpatient Pharmacy Letter • Dear Distributor Letter • Distributor Enrollment Form • Supporting Document	**Sequence 0002**: Edits to Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form*, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray) and minor editorial changes. *The Closed System Pharmacy Enrollment Form was not formally submitted through the Gateway but was submitted via email on May 18, 2012 and included in the June 5, 2012 FDA approval letter.

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Assessment Report 1 at 6 months – due 06/28/2012	**Sequence 0003**: Assessment report covering 12/28/2011 to 04/27/2012
2	November 7, 2013	Draft Documents submitted on or before 09/28/2012 • Chain Pharmacy Enrollment Form • Outpatient Pharmacy Enrollment Form • Closed System Pharmacy Overview • Education Program • Frequently Asked Questions (FAQ) • Outpatient Pharmacy Letter • REMS • Supporting Document	**Sequence 0004**: Modification proposed to: • Incorporate closed system pharmacies into the TIRF REMS Access Program • Correct minor inconsistencies between the FDA provided versions and the current PDF versions of REMS materials
N/A	N/A	Assessment Report 2 at 1 year – due 12/28/2012	**Sequence 0005**: Assessment Report covering 04/28/2012 to 10/28/2012
2	November 7, 2013	Amendment to 09/28/2012 supplement: • Chain Outpatient Pharmacy Enrollment Form • Independent Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient	**Sequence 0006**: Modification proposed to: • Revised terminology, processes, and definitions for outpatient pharmacies • Revised attestations for physicians and patients to address concerns regarding patient access • Revised Program Overview and Frequently Asked Questions to improve clarity and content

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Enrollment Form • Distributor Enrollment Form • Prescriber Enrollment Form	• Updated REMS materials to reflect the completion of the transition phase for the
		• Patient Provider Agreement Form • Chain Outpatient Pharmacy Overview • Independent Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Patient and Caregiver Overview • Prescriber Overview • Education Program • Knowledge Assessment • Frequently Asked Questions (FAQ) • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Healthcare Provide Letter • Dear Distributor Letter • REMS	TIRF REMS Access Program

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Supporting Document • Website Landing Page	
N/A	N/A	Assessment Report 3 at 2 years – due 12/28/2013	**Sequence 0007: Assessment Report covering 10/29/2012 to 10/28/2013**
N/A	N/A	Safety Surveillance Report #1 – due 03/31/2014	**Sequence 0008: Safety surveillance data covering Q4 2012 to Q3 2013**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient	**Sequence 0009**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the currently approved TIRF products list on the FDA Approved REMS website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ	and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and
		• Supporting Document • Website Prototype	• FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed
N/A	N/A	Cash Claim Information Request Response – due 05/30/2014	**Sequence 0010: Response to 5/16/2014 FDA Cash Claim Information Request**
N/A	N/A	DMF Annual Report – due 08/20/2014	**Sequence 0011: DMF Annual Report**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Knowledge Assessment • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient	**Sequence 0012**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the TIRF Products webpage on the TIRF REMS Access website • Updated REMS

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ • Supporting Document • Website Prototype	materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed • Updated Education Program and Knowledge Assessment to incorporate approved labeling supplement

Modification No.	Date Approved	Documents Affected	Overview of Modification
3	December 24, 2014	Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter	**Sequence 0013**: Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter
N/A	N/A	Assessment Report 4 at 3 years – due 12/28/2014	**Sequence 00014: Assessment Report covering 10/29/2013 to 10/28/2014**
N/A	N/A	BioDelivery Sciences International – Letter of Authorization	**Sequence 0015: BioDelivery Sciences International – Letter of Authorization**
N/A	N/A	Actavis Laboratories Inc. – Letter of Authorization	**Sequence 0016: Actavis Laboratories Inc. – Letter of Authorization**
N/A	N/A	DMF Annual Report – due 08/20/2015	**Sequence 0017: DMF Annual Report**
N/A	N/A	36-Month Assessment – Consolidated Information Requests	**Sequence 0018: Response to FDA 36-Month Assessment Information Requests**
N/A	N/A	Assessment Report 5 at 4 years – due 12/28/2015	**Sequence 00019: Assessment Report covering 10/29/2014 to 10/28/2015**
N/A	N/A	Sentnyl Therapeutics, Inc. – Letter of Authorization	**Sequence 00020: Sentnyl Therapeutics, Inc. – Letter of Authorization**
N/A	N/A	Withdraw Authorization for Galena BioPharma, Inc.	**Sequence 00021: Letter of Authorization/Withdrawn Letter of Authorization**

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00022: Administrative Change; Change in US Agent**
N/A	N/A	48-Month REMS Supplemental Assessment Report	**Sequence 00023: 48-Month REMS Supplemental Assessment Report**
N/A	N/A	DMF Annual Report – due 08/20/2016	**Sequence 0024: DMF Annual Report**
N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00025: Administrative Change; Change in US Agent**
NA	N/A	Assessment Report 6 at 5 years – due 12/28/2016	**Sequence 0027: Assessment Report covering 10/29/2015 to 10/28/2016**
N/A	N/A	48-Month FDA Assessment Report Consolidated Information Requests	**Sequence 0026: TIRG REMS Access Program 48-Month FDA Assessment Report Consolidated Responses to FDA Information Requests**

TIRF REMS Access Program
48-Month FDA Assessment Report
Consolidated Information Request DMF Submission

In follow-up to FDA's review of the TIRF REMS Access Program 48-Month FDA Assessment Report, multiple information requests were issued to the TRIG. As previously agreed to by FDA on 25FEB2015, a response to each information request is provided via email with a consolidated information request being submitted to FDA once the Assessment Report Acknowledgement Letter is received.

The complete list of 48-Month FDA Assessment Report information requests and date of each response are shown in the table below. Each individual response is attached.

Information Request	Received	Summary of Request/Correspondence	Response Provided to FDA
1	17MAY2016	• Explanation of the calculations for opioid tolerant and non-opioid tolerant in Tables 3b and 6b (IMS Study titled "TIRF REMS Access Program Assessment Study Report (dated April 22, 2016) included in the Supplemental Report submission) • Clarification of how the N of 9,283 was derived in Table 3b (Persistency Analysis titled "TIRF REMS Persistency Analysis Final Report" included in the Supplemental Report submission)	27MAY2016
2	18JUL2016	• Confirmation of the timeline for the 2016 Knowledge, Attitude, and Behavior (KAB) surveys of prescribers, pharmacists, and patients	20JUL2016
3	21JUL2016	• Confirmation of what FDA requested changes could and could not be incorporated into the KAB survey results slated for submission by 28DEC2016 • Request for FDA to confirm whether all requests should be incorporated into the Assessment Report delaying the submission date until on or before 17FEB2017	28JUL2016
N/A	29JUL2016	• TRIG and FDA agreed to submit the 60-Month FDA Assessment Report on or before 28DEC2016, but delay submission of the KAB survey results until on or before 17FEB2017 to allow for all requested changes to be incorporated into the surveys	01AUG2016
48-Month Acknowledgement Letter	07DEC2016 and 18JAN2017	• TRIG and FDA agreed to a teleconference on 03MAR2017 at 2 PM EST to discuss opportunities for obtaining additional data on accidental exposure in children, as well as 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.	12DEC2016 and 19JAN2017

TIRF REMS Access Program 48-Month FDA Assessment Report

FDA Information Request 1 Response

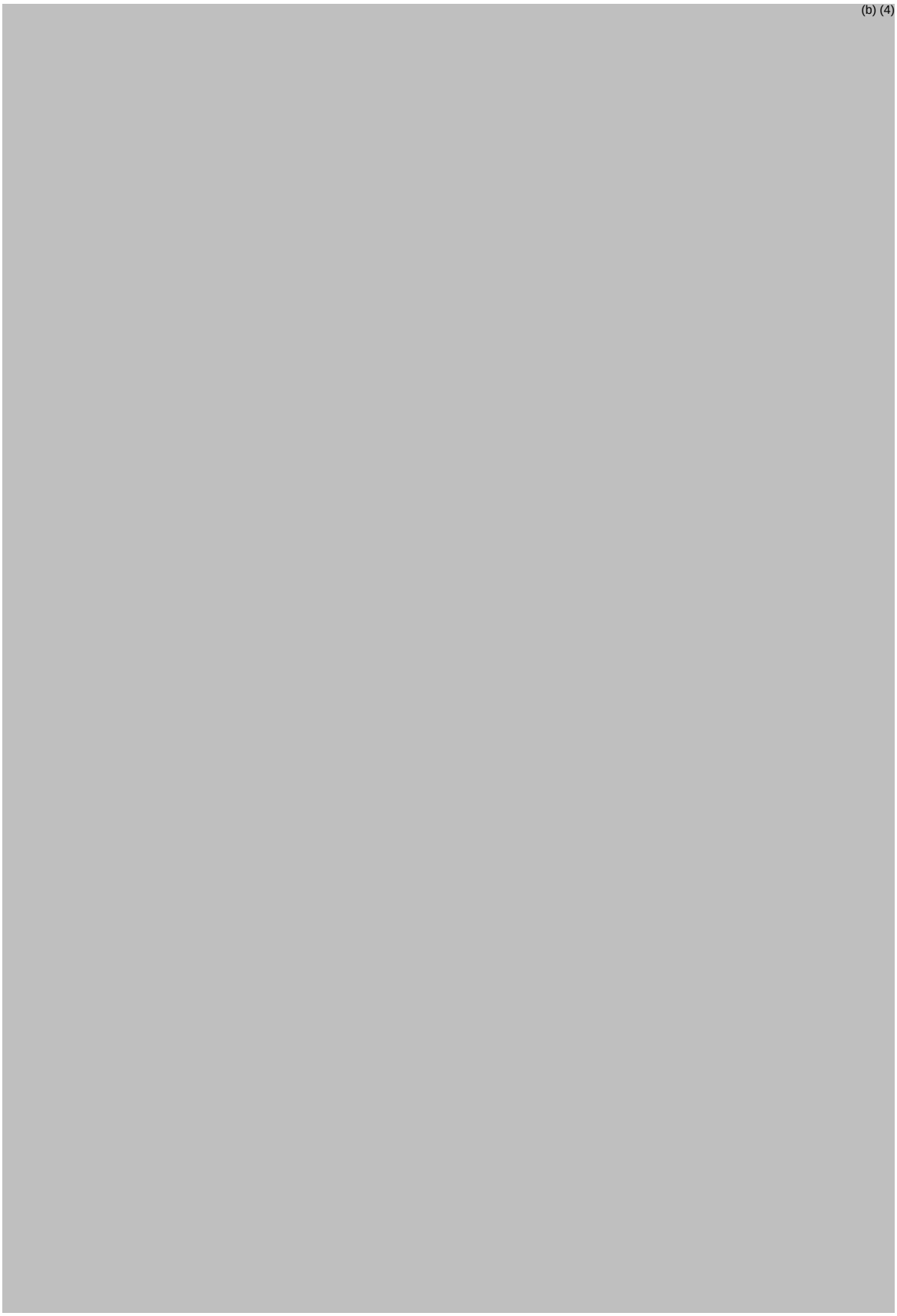
The bold text below represents the FDA requests included in the correspondence dated 17MAY2016. The TRIG's response is shown below each request.

1. **FDA Comment: In your "TIRF REMS Access Program Assessment Study Report" (dated April 22, 2016), provide detailed descriptions as to how the percentages for Opioid-Tolerant and Non-Opioid-Tolerant were calculated in Tables 3b and 6b.**

   TRIG Response: Patients were defined as opioid tolerant if they had an opioid analgesic product prescription fill with at least 7 continuous days of sufficient daily dose immediately preceding the TIRF prescription date. Prior prescriptions of opioid analgesic products were identified as ≥ 1 prescription fill for opioid analgesics within 30 days. To account for combinations of products, sufficient daily dose was calculated by summing the daily dose for each prescription fill. Additional details on definitions and calculations can be found in *Section F. Drug Exposures of the TIRF REMS Access Program Assessment (dated April 22, 2016)*.

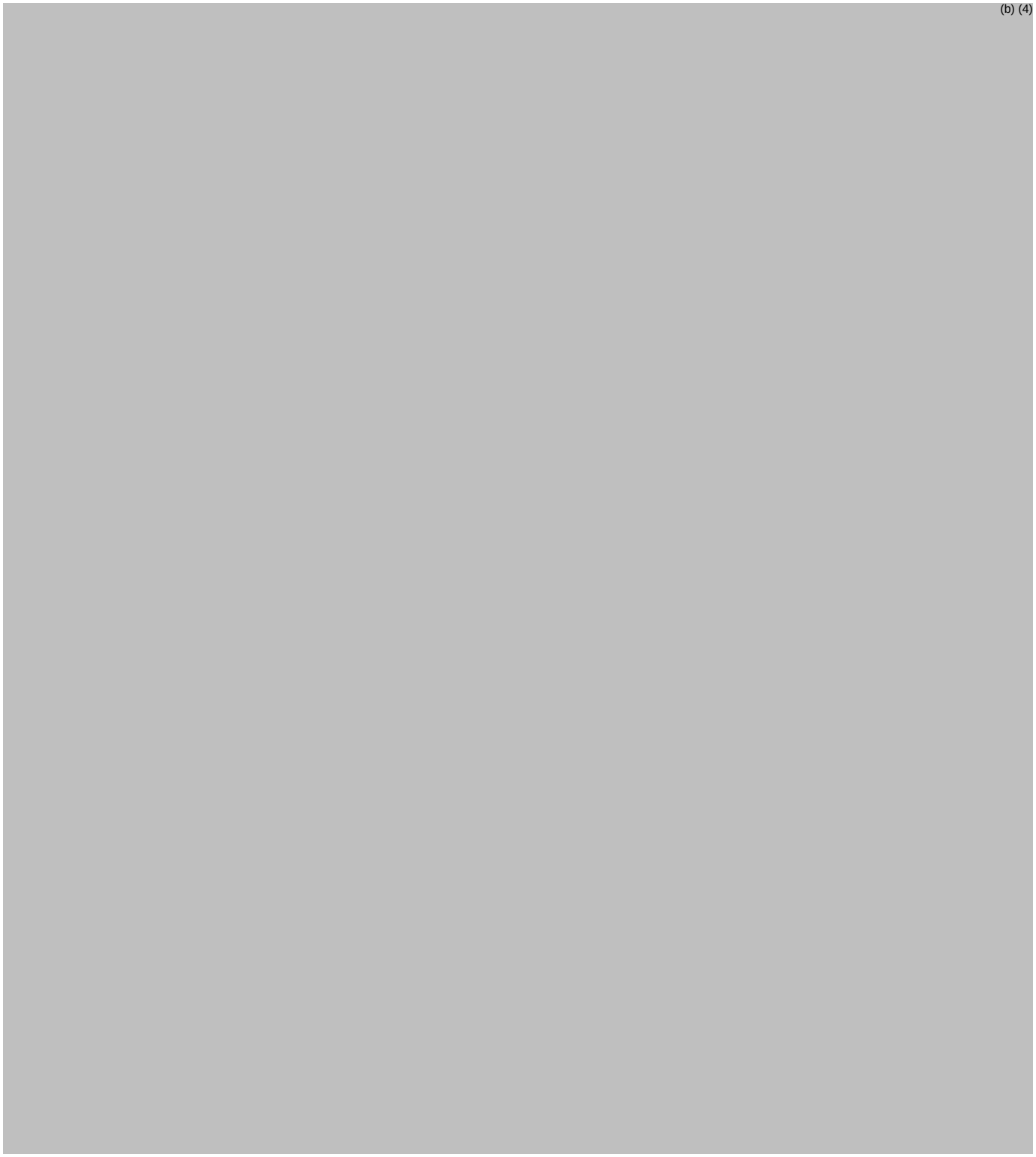
   The percentage of opioid tolerant patients was calculated using the number of opioid tolerant patients divided by the total number of patients who received an initial TIRF prescription (Table 3b: 12,406/25,322= 49.0%). Patients shown as non-opioid tolerant were those who received a TIRF prescription, but had not met the criteria for opioid tolerance (e.g., no previous opioid prescription or insufficient dose/days' supply within the defined time window). The percentage for opioid non-tolerant patients was calculated using the number of non-opioid tolerant patients divided by the number of patients who received an initial TIRF prescription (Table 3b: 12,916/25,322= 51.0%). The same calculation logic for both opioid tolerant patients and non-opioid tolerant patients was used in the sensitivity analysis shown in Table 6b.

(b) (4)



2. (b) (4)

(b) (4)



TIRF REMS Access Program 48-Month FDA Assessment Report

FDA Information Request 2 Response

The bold text below represents the FDA requests included in the correspondence dated 18JUL2016. The TRIG's response is shown below each request.

1. **FDA Comment: Have the surveys for the next assessment started yet?**

   TRIG Response: The 2016 Knowledge, Attitude and Behavior (KAB) surveys for prescribers, pharmacists and patients have not yet launched; however, the Electronic Data Capture (EDC) system is in its formal validation stage.

2. **If not, when is the planned start date for these surveys?**

   TRIG Response: In order to meet the survey completer goals for each survey and submit the finalized reports per the current Timetable for Submission of Assessments, the launch date for the surveys is anticipated to be on or before 05AUG2016. At this time all protocols have been finalized, the patient materials have been IRB approved and the EDC system used is in its formal validation stage.

3. **The DRISK group has some comments on the surveys they would like to have incorporated in the next assessment.**

   TRIG Response: TRIG is open to incorporating these changes. If the changes are minimal, they may be able to be incorporated into the 60-Month FDA Assessment Report for submission in December. Extensive changes or those that necessitate IRB re-review and approval may require a Supplemental Report, a negotiated delay in report submission beyond the 28DEC2016 submission due date, or incorporation into the 2017 KAB Surveys.

TIRF REMS Access Program 48-Month FDA Assessment Report

FDA Information Request 3 Response

The bold text below represents the FDA requests included in the correspondence dated 21JUL2016. The TRIG's response is shown below each request.

1. **FDA Communication: The FDA would like to provide the following comments to the TRIG regarding the TIRF patient, prescriber, and pharmacist surveys. Additional comments on the full 48-month TIRF REMS assessment will be provided in a separate communication. We do not intend to review updates to your survey methodology based on these recommendations prior to the next assessment. Please provide any updated methodology with your next assessment submission.**

   In addition, within the next 7 days and before starting the survey, let us know if the recommended changes are able to be incorporated or if IRB re-review is needed. If IRB re-review is required, provide a timeline of how much additional time is needed.

   TRIG Response: The TRIG has carefully reviewed the 21JUL2016 FDA correspondence and has determined that there are some changes that can be readily accommodated and others which will require more substantial changes to the EDC system. In order to reach the survey completer goal and submit the 60-Month FDA Assessment Report as required on or before 28DEC2016, TRIG can incorporate the 5 requests shown in Table 1. These changes are updates to existing questions or small protocol updates. While these updates would delay launch of the survey past the original milestone of 05AUG2016, the TRIG anticipates still being able to meet the survey completer goals and a timely report submission on or before 28DEC2016.

   The time to incorporate the remaining 11 requests (Table 2) related to adding survey questions and changing inclusion criteria for pharmacists and prescribers would put in jeopardy the TRIG's ability to meet survey completer goals and submit the report on or before 28DEC2016. The TRIG has identified two possible options for handling the requested changes. **The TRIG requests that FDA provide their preference on the below approach options by close of business (COB) Eastern Standard Time (EST) 04AUG2016.**

   The TRIG believes that by incorporating all changes provided in the 21JUL2016 FDA correspondence prior to launch of the 2016 surveys and delaying submission of the 60-Month FDA Assessment Report by 45 days (target submission on or before 17FEB2017), it would provide the most comprehensive and timely response to the Agency's request; therefore, TRIG recommends this approach.

   Alternatively, the TRIG could incorporate only the items listed below in Table 1 and provide them in the 60-Month FDA Assessment Report to be submitted on or before 28DEC2016. The remaining requests outlined in the 21JUL2016 correspondence (Table 2) would be incorporated into the 2017 KAB Surveys.

Table 1. FDA Requests that Can Be Incorporated for 28DEC2016 Submission

Stakeholder	FDA Feedback*	TRIG Response
Patient	B. Under Key Risk Message 2: Revised question "*TIRF medicines should only be taken by cancer patients who are opioid tolerant*". Return to the original question used in the previous surveys, "*TIRF medicines should only be taken by patients who are opioid tolerant*."	Question 11 will be updated to remove reference to "cancer" Changes to the patient protocol and survey require IRB review prior to launch (approximately 5 days) Change requires re-validation of the EDC system (approximately 4-6 weeks). **[The Electronic Data Capture (EDC) system used in the TRIG KAB Surveys is a regulatory compliant/Part 11 compliant system. Application changes after validation begins include regression analysis, regulatory assessment, documentation of requirements, coding, code review and unit testing, and formal validation to ensure the changes are implemented as expected, and there is no unforeseen impact to the survey functionality.]**
Patient	D. FDA recommends revisions to the questions that ask patients about prescriber activities to allow pharmacists as a potential source of information. Revise question that begin with: *Did the doctor, nurse, or other healthcare professional in the doctor's office ever....* to: *Did a doctor, nurse, or other healthcare professional ever....* • talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? • tell you how to use the TIRF medicine that was most recently prescribed for you? • tell you how to store or keep the TIRF medicine that was most recently prescribed for you?	Questions 9, 15, and 16 will be updated to change "the" to "a" Changes to the patient protocol and survey require IRB review prior to launch (approximately 5 days) Changes require re-validation of the EDC system (approximately 4-6 weeks). [See Table 1, Patient Item B bolded item for validation explanation]
Pharmacist	A. There were no closed system pharmacy (CSP) survey respondents. In addition, the FDA asked the sponsor to recruit more non-supervisory pharmacists. The sponsor reported that despite recruitment efforts, only 18% reported that they were not the pharmacist in charge. FDA recommends the sponsor to continue efforts to recruit closed system pharmacy survey respondents and recruit more non-supervisory pharmacists as survey respondents.	TRIG will attempt to recruit more CSP and non-supervisory pharmacist survey respondents

Stakeholder	FDA Feedback*	TRIG Response
Pharmacist	F. Provide a description of how pharmacies that dispense TIRF medicines compare to the pharmacies represented by survey respondents. If possible, provide what percentage of orders are from outpatient vs. inpatient vs. closed system pharmacies. In addition for the survey respondents, provide additional information about if multiple regions represented, how many pharmacists were from the same pharmacies, and how many pharmacies were represented in the survey.	TRIG will update the analysis as requested
Prescriber	C. Revise the question: *For which indications do you prescribe TIRF medicines to opioid tolerant patients.* This assumes prescribers are only using TIRF medicines for opioid tolerant patients which may not be the case. Example Revision: *Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed*? to opioid tolerant patients?	TRIG will revise Question 9 to remove reference to opioid tolerant patients Change requires re-validation of the EDC system (approximately 4-6 weeks). [See Table 1, Patient Item B bolded item for validation explanation]

* Referenced lettering corresponds with the 21JUL2016 FDA correspondence.

Table 2. FDA Requests That Cannot be Incorporated for 28DEC2016 Submission

Stakeholder	FDA Feedback*	TRIG Response
Patient	A. Add question: A side effect of TIRF medicines is the chance of abuse or addiction.	Changes to the patient protocol and survey require IRB review prior to launch (approximately 5 days) Change requires EDC to be modified to add a question In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.
Patient	C. Add questions under Key Risk Message 5. Example questions: • TIRF medicines can be misused by people who abuse prescription medicines or street drugs. • Keep the TIRF medicine in a safe place to prevent it from being stolen.	Changes to the patient protocol and survey require IRB review prior to launch (approximately 5 days) Changes require EDC to be modified to add questions In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.
Patient	E. The questions in the patient survey about healthcare professional or prescriber activities do not correspond to the questions included in the prescriber and pharmacist survey. FDA recommends alignment of these questions. In the patient survey, include additional questions about the following: • Did a doctor, nurse, or other healthcare professional ever ask you about the presence of children in the home. • Did a doctor, nurse, or other healthcare professional ever tell you not to share the TIRF medicines with anyone else. • Did a doctor, nurse, or other healthcare professional ever counsel you that accidental exposure to TIRF medicines by a child may be fatal • Did a doctor, nurse, or other healthcare professional ever tell you to keep TIRF medicines out of reach of children to prevent	Changes to the patient protocol and survey require IRB review prior to launch (approximately 5 days) Changes require EDC to be modified to add questions In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.

Stakeholder	FDA Feedback*	TRIG Response
	accidental exposure. • Did a doctor, nurse, or other healthcare professional ever tell you about proper disposal of any unused or partially used TIRF medicines.	
Pharmacist	B. Thirty-nine percent (39%) of respondents had not dispensed TIRF medicines within the last six months. FDA recommends limiting the survey to pharmacists who have dispensed TIRF medicines in the past six months.	Requires changes to recruitment process and materials
Pharmacist	C. The questions in the pharmacist survey about pharmacists' reported activities do not correspond to the questions included in the patient survey. FDA recommends alignment of these questions In the pharmacist survey, include additional questions about the following: • How frequently do you perform the following activities when dispensing TIRF medicines? • Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed? • Instruct the patient on how to use the TIRF medicine that was most recently prescribed? • Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed?	Changes require EDC to be modified to add questions In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.
Pharmacist	D. Add question from patient survey to pharmacist survey to Key Risk Message 1: *TIRF medicines should only be taken by cancer patients who are opioid tolerant. (T/F/DK)*	Change requires EDC to be modified to add a question In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.
Pharmacist	E. Add a question to assess pharmacists' awareness of the REMS risk for TIRFs (misuse, abuse, addiction, overdose, medication errors). Example question: *Which of the following risks are associated with the use of Transmucosal immediate release fentanyl (TIRF) medicines*? [Add foils]: • Misuse (T/F/DK) • Abuse (T/F/DK) • Addiction (T/F/DK)	Changes require EDC to be modified to add questions In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.

Stakeholder	FDA Feedback*	TRIG Response
	• Overdose (T/F/DK)	
Prescriber	A. Twenty-one percent (25%) of respondents stated that they had not prescribed a TIRF medicine within the last six months. FDA recommends limiting survey respondents to prescribers who have prescribed TIRF medicines in the past 6 months.	Requires changes to recruitment process and materials
Prescriber	B. Add question from patient survey to prescriber survey to Key Risk Message 1: *TIRF medicines should only be taken by cancer patients who are opioid tolerant. (T/F/DK)*	Change requires EDC to be modified to add a question In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.
Prescriber	D. The questions in the prescriber survey about prescriber reported activities do not correspond to the questions included in the patient survey. FDA recommends alignment of these questions. In the prescriber survey, include additional questions about the following: • *How frequently do you perform the following activities when prescribing TIRF medicines?* ○ Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed? ○ Instruct the patient on how to use the TIRF medicine that was most recently prescribed? ○ Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed?	Changes require EDC to be modified to add questions In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.
Prescriber	E. Add a question to assess prescriber's awareness of the REMS risks for TIRF medicines (misuse, abuse, addiction, overdose). Example question: *Which of the following risks are associated with the use of Transmucosal immediate release fentanyl (TIRF) medicines*? [Add foils]: • Misuse (T/F/DK) • Abuse (T/F/DK) • Addiction (T/F/DK) • Overdose (T/F/DK)	Changes require EDC to be modified to add questions In addition to, but prior to validation, application development lifecycle processes must be followed for these changes. The 21JUL2016 FDA correspondence was received after the application development process was complete for all 3 TRIG Surveys.

* Referenced lettering corresponds with the 21JUL2016 FDA correspondence.

TIRF REMS Access Program 48-Month FDA Assessment Report

FDA & TRIG Correspondence (29JUL2016-01AUG2016)

Dinesh Anugu

From: Brown, Wendy <Wendy.Brown@fda.hhs.gov>
Sent: Monday, August 01, 2016 12:47 PM
To: Dinesh Anugu
Cc: Bulkley, Amanda; Sremba, Siressa (Siressa.Sremba@McKesson.com)
Subject: RE: Submission Proposal | INFORMATION REQUEST #3: 48-month, TIRF REMS Assessment

Hi Dinesh,

I have forwarded the response provided to our DRISK Assessment team and will get back to you if there are additional comments or questions.

Thanks,
WENDY

WENDY B. BROWN, PHARMD, BCACP | Safety Regulatory PM
FDA/OMPT/CDER/OSE/PMS | 10903 New Hampshire Ave
WO22 RM4484 | Silver Spring, MD 20993
Office: 240-402-9140 | BB: 240-731-8615
Email: wendy.brown@fda.hhs.gov

From: Dinesh Anugu [mailto:danugu@insysrx.com]
Sent: Monday, August 01, 2016 3:02 PM
To: Brown, Wendy
Cc: Bulkley, Amanda; Sremba, Siressa (Siressa.Sremba@McKesson.com)
Subject: RE: Submission Proposal | INFORMATION REQUEST #3: 48-month, TIRF REMS Assessment

Dear Wendy,

In response to the Agency's options provided below for the 48-month TIRF REMS Assessment, TRIG agrees with FDA's approach of submission of all items in the assessment plan except the surveys on the December due date, and submission of the surveys February 17th.

Please let me know if you have any further questions.

Thank you,
Dinesh

Dinesh Reddy Anugu, MS, RAC
Regulatory Affairs Associate

1333 South Spectrum Blvd, Suite 100., Chandler, AZ 85286
P: (480) 500-3193 F: (602) 910-2627
danugu@insysrx.com* www.insysrx.com

From: Brown, Wendy [mailto:Wendy.Brown@fda.hhs.gov]
Sent: Friday, July 29, 2016 5:33 AM
To: Dinesh Anugu <danugu@insysrx.com>
Cc: Bulkley, Amanda <amanda.bulkley@mckesson.com>; Sremba, Siressa (Siressa.Sremba@McKesson.com) <Siressa.Sremba@McKesson.com>
Subject: Submission Proposal | INFORMATION REQUEST #3: 48-month, TIRF REMS Assessment

Hi Dinesh,

In response to your proposal, provided on 7/28, via email, the Agency would like the TRIG to consider the following option(s) for submission of the 48-month, TIRF REMS Assessment:

1. Submission of all items in the assessment plan except the surveys on the December due date.
2. Submission of the surveys February 17th

This essentially splits the submission, however, we have done this in the past for other assessments. In the case of the TIRF REMS, there is so much data included in the report outside of the surveys that we'd really prefer to begin working on those sections of the assessment in late December/early January.

Additionally, there is one *correction* to a survey comment provided in the 7/21 IR via email:

- **Original Comment:** Add question from patient survey to prescriber and pharmacist survey to Key Risk Message 1: *TIRF medicines should only be taken by cancer patients who are opioid tolerant. (T/F/DK)*

- **Additional Comment:** Please ensure that the added question is the proposed revised question: TIRF medicines should only be taken by ~~cancer~~ patients who are opioid-tolerant. *(T/F/DK)*

Please provide response **by COB, Thursday, August 4**.

Thanks,
WENDY

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Email: wendy.brown@fda.hhs.gov

From: Brown, Wendy
Sent: Thursday, July 28, 2016 5:07 PM
To: 'Dinesh Anugu'
Cc: Bulkley, Amanda; Sremba, Siressa (Siressa.Sremba@McKesson.com)
Subject: RE: INFORMATION REQUEST #3: 48-month, TIRF REMS Assessment

Hi Dinesh,

I have forwarded this information to our DRISK Assessment team for review and will provide their response, as requested, by COB, Thursday, AUGUST 4.

Thanks,
WENDY

WENDY B. BROWN, PHARMD, BCACP | Safety Regulatory PM
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Email: wendy.brown@fda.hhs.gov

From: Dinesh Anugu [mailto:danugu@insysrx.com]
Sent: Thursday, July 28, 2016 4:49 PM
To: Brown, Wendy
Cc: Bulkley, Amanda; Sremba, Siressa (Siressa.Sremba@McKesson.com)
Subject: RE: INFORMATION REQUEST #3: 48-month, TIRF REMS Assessment

Dear Wendy,

Please find attached the TRIG's response for the below Information request# 3.

Also, TRIG is requesting for response on FDA's preference on the TRIG's approach (Please see attached document) by close of business (COB) Eastern Standard Time (EST) **04AUG2016**.

Let me know if you have any further questions.

Thank you,
Dinesh

Dinesh Reddy Anugu, MS, RAC
Regulatory Affairs Associate

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danugu@insysrx.com* www.insysrx.com

From: Brown, Wendy [mailto:Wendy.Brown@fda.hhs.gov]
Sent: Thursday, July 21, 2016 7:22 AM
To: Dinesh Anugu <danugu@insysrx.com>
Cc: Bulkley, Amanda <amanda.bulkley@mckesson.com>; Sremba, Siressa (Siressa.Sremba@McKesson.com) <Siressa.Sremba@McKesson.com>
Subject: INFORMATION REQUEST #3: 48-month, TIRF REMS Assessment

Hi Dinesh,

The FDA would like to provide the following comments to the TRIG regarding the TIRF patient, prescriber, and pharmacist surveys. Additional comments on the full 48-month TIRF REMS assessment will be provided in a separate communication. We do not intend to review updates to your survey methodology based on these recommendations prior to the next assessment. Please provide any updated methodology with your next assessment submission.

In addition, **within the next 7 days and before starting the survey**, let us know if the recommended changes are able to be incorporated or if IRB re-review is needed. If IRB re-review is required, provide a timeline of how much additional time is needed.

TIRF REMS Survey Comments

1. Patient Survey Comments

A. Add question: A side effect of TIRF medicines is the chance of abuse or addiction.

B. Under Key Risk Message 2: Revised question "*TIRF medicines should only be taken by cancer patients who are opioid tolerant*". Return to the original question used in the previous surveys, "*TIRF medicines should only be taken by patients who are opioid tolerant*."

C. Add questions under Key Risk Message 5. Example questions:
- TIRF medicines can be misused by people who abuse prescription medicines or street drugs.
- Keep the TIRF medicine in a safe place to prevent it from being stolen.

D. FDA recommends revisions to the questions that ask patients about prescriber activities to allow pharmacists as a potential source of information. Revise question that begin with: *Did the doctor, nurse, or other healthcare professional in the doctor's office ever....* to: *Did a doctor, nurse, or other healthcare professional ever*....
- talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you?
- tell you how to use the TIRF medicine that was most recently prescribed for you?
- tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

E. The questions in the patient survey about healthcare professional or prescriber activities do not correspond to the questions included in the prescriber and pharmacist survey. FDA recommends alignment of these questions. In the patient survey, include additional questions about the following:
- Did a doctor, nurse, or other healthcare professional ever ask you about the presence of children in the home.

- Did a doctor, nurse, or other healthcare professional ever tell you not to share the TIRF medicines with anyone else.
- Did a doctor, nurse, or other healthcare professional ever counsel you that accidental exposure to TIRF medicines by a child may be fatal
- Did a doctor, nurse, or other healthcare professional ever tell you to keep TIRF medicines out of reach of children to prevent accidental exposure.
- Did a doctor, nurse, or other healthcare professional ever tell you about proper disposal of any unused or partially used TIRF medicines.

2. Pharmacist Survey Comments

A. There were no closed system pharmacy (CSP) survey respondents. In addition, the FDA asked the sponsor to recruit more non-supervisory pharmacists. The sponsor reported that despite recruitment efforts, only 18% reported that they were not the pharmacist in charge. FDA recommends the sponsor to continue efforts to recruit closed system pharmacy survey respondents and recruit more non-supervisory pharmacists as survey respondents.

B. Thirty-nine percent (39%) of respondents had not dispensed TIRF medicines within the last six months. FDA recommends limiting the survey to pharmacists who have dispensed TIRF medicines in the past six months.

C. The questions in the pharmacist survey about pharmacists' reported activities do not correspond to the questions included in the patient survey. FDA recommends alignment of these questions In the pharmacist survey, include additional questions about the following:
   - *How frequently do you perform the following activities when dispensing TIRF medicines?*
     - Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed?
     - Instruct the patient on how to use the TIRF medicine that was most recently prescribed?
     - Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed?

D. Add question from patient survey to pharmacist survey to Key Risk Message 1: *TIRF medicines should only be taken by cancer patients who are opioid tolerant. (T/F/DK)*

E. Add a question to assess pharmacists' awareness of the REMS risk for TIRFs (misuse, abuse, addiction, overdose, medication errors). Example question: *Which of the following risks are associated with the use of Transmucosal immediate release fentanyl (TIRF) medicines*? [Add foils]:
   - Misuse (T/F/DK)
   - Abuse (T/F/DK)
   - Addiction (T/F/DK)
   - Overdose (T/F/DK)

F. Provide a description of how pharmacies that dispense TIRF medicines compare to the pharmacies represented by survey respondents. If possible, provide what percentage of orders are from outpatient vs. inpatient vs. closed system pharmacies. In addition for the survey respondents, provide additional information about if multiple regions represented, how many pharmacists were from the same pharmacies, and how many pharmacies were represented in the survey.

3. Prescriber Survey Comments

A. Twenty-one percent (25%) of respondents stated that they had not prescribed a TIRF medicine within the last six months. FDA recommends limiting survey respondents to prescribers who have prescribed TIRF medicines in the past 6 months.

B. Add question from patient survey to prescriber survey to Key Risk Message 1: *TIRF medicines should only be taken by cancer patients who are opioid tolerant. (T/F/DK)*

C. Revise the question: *For which indications do you prescribe TIRF medicines to opioid tolerant patients.* This assumes prescribers are only using TIRF medicines for opioid tolerant patients which may not be the case. Example Revision: *Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed*? to opioid tolerant patients?

D. The questions in the prescriber survey about prescriber reported activities do not correspond to the questions included in the patient survey. FDA recommends alignment of these questions. In the prescriber survey, include additional questions about the following:
   - *How frequently do you perform the following activities when prescribing TIRF medicines?*
     - Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed?
     - Instruct the patient on how to use the TIRF medicine that was most recently prescribed?
     - Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed?

E. Add a question to assess prescriber's awareness of the REMS risks for TIRF medicines (misuse, abuse, addiction, overdose). Example question: *Which of the following risks are associated with the use of Transmucosal immediate release fentanyl (TIRF) medicines*? [Add foils]:
   - Misuse (T/F/DK)
   - Abuse (T/F/DK)
   - Addiction (T/F/DK)
   - Overdose (T/F/DK)

Please contact us if there are any questions about the above recommendations.

Thanks,
WENDY

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Email: wendy.brown@fda.hhs.gov

From: Brown, Wendy
Sent: Wednesday, July 20, 2016 12:18 PM
To: 'Dinesh Anugu'
Cc: Bulkley, Amanda; Sremba, Siressa (Siressa.Sremba@McKesson.com)
Subject: RE: INFORMATION REQUEST #2: 48-month, TIRF REMS Assessment

Hi Dinesh,

I appreciate you providing your response so quickly. I have forwarded this information to the team and will get back to you with any additional questions, if received.

Thanks,
WENDY

WENDY B. BROWN, PHARMD, BCACP | Safety Regulatory PM
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WO22 RM4484 | Silver Spring, MD 20993
Office: 240-402-9140 | BB: 240-731-8615
Email: wendy.brown@fda.hhs.gov

From: Dinesh Anugu [mailto:danugu@insysrx.com]
Sent: Wednesday, July 20, 2016 11:03 AM
To: Brown, Wendy
Cc: Bulkley, Amanda; Sremba, Siressa (Siressa.Sremba@McKesson.com)
Subject: RE: INFORMATION REQUEST #2: 48-month, TIRF REMS Assessment

Dear Wendy,

Please find attached the TRIG response for the below Information request. Let me know if you have any further questions.

Thank you,
Dinesh Anugu

Dinesh Reddy Anugu, MS, RAC
Regulatory Affairs Associate

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danugu@insysrx.com* www.insysrx.com

From: Brown, Wendy [mailto:Wendy.Brown@fda.hhs.gov]
Sent: Monday, July 18, 2016 12:02 PM
To: Dinesh Anugu <danugu@insysrx.com>
Cc: Bulkley, Amanda <amanda.bulkley@mckesson.com>
Subject: INFORMATION REQUEST #2: 48-month, TIRF REMS Assessment

Hi Dinesh,

Our team is requesting response to the following questions, **by COB, Wednesday, July 20**:

- Have the surveys for the next assessment started yet?

- If *not*, when is the planned start date for these surveys?

The DRISK group has some comments on the surveys they would like to have incorporated in the next assessment.

Please let me know if you have questions.

Thanks,
WENDY

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TIRF REMS Access Program 48-Month FDA Assessment Report

FDA Acknowledgement Letter Correspondence

Dinesh Anugu

From: Brown, Wendy <Wendy.Brown@fda.hhs.gov>
Sent: Thursday, January 19, 2017 8:59 AM
To: Dinesh Anugu
Cc: Bulkley, Amanda (amanda.bulkley@mckesson.com)
Subject: RE: T-Con RESCHEDULE: Receipt of the 48-Month FDA Acknowledgement Letter-TRIG

Hi Dinesh,

I appreciate you confirming that this date and time will work for your group. I will solidify this on our calendars and await receipt of your WebEx and call-in information, as appropriate.

Thanks so much,
WENDY

Wendy B. Brown, PharmD, BCACP
Safety Regulatory Project Manager

Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-9140 | BB: 240-731-8615
wendy.brown@fda.hhs.gov

From: Dinesh Anugu [mailto:danugu@insysrx.com]
Sent: Thursday, January 19, 2017 10:01 AM
To: Brown, Wendy
Cc: Bulkley, Amanda (amanda.bulkley@mckesson.com)
Subject: RE: T-Con RESCHEDULE: Receipt of the 48-Month FDA Acknowledgement Letter-TRIG

Good Morning Wendy,

I have confirmed with the TRIG and **FRIDAY, MARCH 3 @ 2:00 PM EST** will work for the meeting with FDA.

Thank you,
Dinesh

Dinesh Reddy Anugu, MS, RAC
Regulatory Affairs Associate

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danugu@insysrx.com* www.insysrx.com

From: Brown, Wendy [mailto:Wendy.Brown@fda.hhs.gov]
Sent: Wednesday, January 18, 2017 7:56 AM
To: Dinesh Anugu <danugu@insysrx.com>
Cc: Bulkley, Amanda (amanda.bulkley@mckesson.com) <amanda.bulkley@mckesson.com>
Subject: T-Con RESCHEDULE: Receipt of the 48-Month FDA Acknowledgement Letter-TRIG
Importance: High

Hi Dinesh,

We've had some scheduling changes on our side and the FEB 22 date & time will no longer work. Please let me know if your group would be available for **FRIDAY, MARCH 3 @ 2:00 PM EST**.

Thanks,
WENDY

Wendy B. Brown, PharmD, BCACP
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Project Management Staff
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Center for Drug Evaluation and Research
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wendy.brown@fda.hhs.gov

From: Dinesh Anugu [mailto:danugu@insysrx.com]
Sent: Monday, December 12, 2016 10:21 AM
To: Brown, Wendy
Cc: Bulkley, Amanda (amanda.bulkley@mckesson.com)
Subject: RE: Receipt of the 48-Month FDA Acknowledgement Letter-TRIG

Dear Wendy,

I would like to confirm **Wednesday, February 22, 2017 @ 3:00 PM EST** for the meeting with FDA.

Please let me know if you have any questions.

Thank you,
Dinesh

Dinesh Reddy Anugu, MS, RAC
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danugu@insysrx.com* www.insysrx.com

From: Brown, Wendy [mailto:Wendy.Brown@fda.hhs.gov]
Sent: Wednesday, December 07, 2016 6:30 AM
To: Dinesh Anugu <danugu@insysrx.com>
Cc: Bulkley, Amanda (amanda.bulkley@mckesson.com) <amanda.bulkley@mckesson.com>
Subject: RE: Receipt of the 48-Month FDA Acknowledgement Letter-TRIG

Hi Dinesh,

I appreciate you following up regarding the request for a meeting. Please let me know which of the dates & times below will work for your group:

- Friday, February 17, 2017 @ 12:30 PM EST
- Wednesday, February 22, 2017 @ 3:00 PM EST

Thanks,
WENDY

Wendy B. Brown, PharmD, BCACP
Safety Regulatory Project Manager

Project Management Staff
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wendy.brown@fda.hhs.gov

From: Dinesh Anugu [mailto:danugu@insysrx.com]
Sent: Friday, December 02, 2016 3:06 PM
To: Brown, Wendy
Cc: Bulkley, Amanda (amanda.bulkley@mckesson.com)
Subject: Receipt of the 48-Month FDA Acknowledgement Letter-TRIG

Dear Wendy,

The TRIG confirms receipt of the 48-Month FDA Acknowledgement Letter. Based on the feedback provided, we are currently working to provide requested data with the February 17, 2017 submission of the 60-month REMS Assessment survey results. The TRIG acknowledges that FDA has requested a meeting to discuss opportunities for obtaining additional data on accidental exposure in children, as well as 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. The TRIG would like to propose that the meeting occur in February, 2017.

Please let me know if you have any questions.

Have a nice weekend!

Thank you,
Dinesh

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