Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW
Interim Comments #1

Date: October 20, 2014

Reviewer(s): Cathy A. Miller, MPH, BSN, Risk Management Analyst
Division of Risk Management (DRISK)
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Table 1

Drug Names, Dosage Form and Sponsor:

Drug Name	Dosage Form and Route	NDA Number	Sponsor
Abstral (fentanyl)	Sublingual tablet	022510	Galenya BioPharma
Actiq (fentanyl citrate)	Oral transmucosal lozenge	020747	Cephalon, Inc.
Fentora and Authorized Generic (fentanyl citrate)	Buccal tablet	021947	Cephalon, Inc.
Lazanda (fentanyl)	Nasal spray	022569	DepoMed, Inc.
Onsolis (fentanyl)	Buccal soluble film	022266	Meda Pharmaceuticals
Subsys (fentanyl)	Sublingual spray	202788	Insys Therapy

Therapeutic class: Opioid Agonist

Dosage forms: Transmucosal Immediate release Fentanyl (TIRF)

Table 2: TIRF REMS Modification #3 DMF 27320 Seq. No. 0009 received May 20, 2014			
Drug Name	**NDA Number**	**Suppl. Submitted Date; Amendment Submitted Date**	**Suppl. Number (Seq. No.)**
Abstral	022510	May 21, 2014	S-014 (0089)
Actiq	020747	May 21, 2014	S-041 (0041)
Fentora and AG	021947	May 21, 2014	S-022 (0048)
Lazanda	022569	May 21, 2014	S-020 (0115)
Onsolis	022266	May 21, 2014	S-014 (0120)
Subsys	202788	May 20, 2014	S-012 (0081)
Abbreviations: *Amend.=Amendment; AG=Authorized Generic; DMF=Drug Master File; LOA=Letter of Authorization; Seq. No.=Sequence Number; Suppl.=Supplement; NDA=New Drug Application*			

OND Review Division: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

OSE RCM #: 2014-2057

TSI #: 290

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n/a = not applicable

1 INTRODUCTION

This is a review of the proposed risk evaluation and mitigation strategy (REMS) modification for the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Single Shared System (SSS) submitted by the Transmucosal REMS Industry Group (TRIG) between March 12 and May 21, 2014 (see Table 2 on cover page 2 for detailed submission information).

1.1 BACKGROUND

TIRF medicines are short-acting fentanyl products indicated for the management of breakthrough pain in adults with cancer who are routinely taking other opioid pain medicines around-the-clock for pain.

The approved TIRF medicines include:

- Abstral (fentanyl) sublingual tablet
- Actiq (fentanyl citrate) oral transmucosal lozenge
- Fentora (fentanyl citrate) buccal tablet
- Lazanda (fentanyl) nasal spray,
- Onsolis (fentanyl) buccal soluble film
- Subsys (fentanyl) sublingual spray
- Approved generic equivalents of these products

The TIRF medicines are approved under a single shared system REMS that has the following goal and objectives:

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 elements included in the program are Medication Guides (MG) for each individual TIRF medicine and the following elements to assure safe use (ETASU):

- Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified
- TIRF medicines will only be dispensed by pharmacies that are specially certified

- TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

The timetable for submission of TIRF REMS Access Program assessments is at 6 and 12 months from the date of the initial REMS approval, and annually thereafter.

1.2 REGULATORY HISTORY

As described in the DRISK December 2011 REMS review[1], FDA determined that all TIRF products were required to have a REMS to ensure that the benefits of the drug outweighed the increased risks of misuse, abuse, addiction, overdose and serious complications due to medication errors. The SSS TIRF REMS program was approved on December 28, 2011, and REMS modifications were approved on June 5, 2012[2] and November 7, 2013[3]. The currently approved TIRF REMS consists of a MG, ETASU, an implementation system, and a timetable for submission of assessments of the REMS.

The regulatory history associated with this proposed TIRF REMS modification is as follows:

On May 20, 2014, the TIRF SSS REMS Sponsors submitted proposed modifications to the REMS for review and consideration to DMF 27320, following communications between the TIRF REMS Industry Group (TRIG) and Vaishali Jarral, Officer of Surveillance and Epidemiology (OSE) Project Manager that were a result of internal discussions about select elements of the TIRF REMS Program[4]:

- **On February 5, 2014, FDA** communicated to the TRIG, via email, suggestions for the next TIRF REMS Modification (#3) which had been discussed during previous months with the workgroup. The purpsose of these changes were to minimize administrative redundancy when revisions to individual TIRF products labeling or packaging occur (see Appendix A) :
    - Removing NDC numbers from TIRF REMS Pharmacy Enrollment Forms
    - Removing 'Attachment A' from the TIRF REMS document and all TIRF appended materials. This request also included a recommendation to add a page to the TIRF REMS Access Program website containing a listing of currently approved TIRF REMS products, Sponsor Names, Contact phone numbers and link to product specific information for each product, as well as the statement "The TRIG attests that the table will only include

[1] DRISK Final TIRF REMS Review December 27, 2011 (G. Toyserkani)

[2] DRISK TIRF REMS Modification #1 Review DARRTS June 1, 2012 (M. Moncur)

[3] DRISK TIRF REMS Modification #2 Review DARRTS October 31, 2013 (K. Lehrfeld)

[4] The TIRF Implementation Workgroup is an internal group of FDA staff from the DRISK, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP), the Office of Center Director (OCD), the Office of Compliance (OC) and the Office of Generic Drugs (OGD) who meet biweekly to discuss current issues pertaining to the TIRF REMS Access Program.

products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website".

- Remove reference to generics for individual products, replacing instead with an asterisk/footnote that the table includes approved generic equivalents of the covered products, in Table 1 of the Education Program.

- **On February 18, 2014**, the TRIG responded to the 2/8/2014 email (See Appendix B) and accepted all requested revisions. In addition, as previously discussed and agreed upon between the Agency and the TRIG during the review of the TIRF REMS 12-Month Assessment report[5] , the TRIG proposed removal of language from the REMS Supporting Document about deactivation of patients shown to have multiple prescribers in an overlapping timeframe due to concerns of non-compliance. The TRIG explained that they have a limited view of data and is unable to confirm or rule out doctor-shopping behavior because it may result in legitimate patient-access issues.

- **On March 24, 2014** the TRIG sent an email communication that included the previously agreed upon TIRF REMS modifications along with the following additional proposed modifications:

  - Revised/editted select language in the Patient Counseling section of the Education Program to strengthen certain information about converting from one TIRF medicine to a different TIRF medicine, and emphasizing TIRF medicines are not equivalent to any other fentanyl product, including TIRF medicines, on a microgram-per-microgram basis, except generic equivalents, based on KAB survey results

  - Revised the Outpatient Pharmacy Overview document and Frequently Asked Questions (FAQs) with added information about the TIRF REMS Cash Claim process, including defining a Cash Claim, and how to correctly process these claims through TIRF REMS Access Program using the REMS Cash BIN 014780.

  - Revised the TIRF REMS Access Program website per agreed upon TIRF REMS modifications agreed upon and outlined above.

  - Revised assessment metrics with FDA/TRIG agreed upon metrics[6]

- **On April 22, 2014,** Office of Surveillance and Epidemiology (OSE) sent an email communication to the TRIG that acknowledged receipt of the proposed TIRF REMS Modifications to-date, and provided instructions for formally submitting a REMS Modification.

[5] DRISK 12-Month TIRF REMS Assessment Report DARRTS October 16, 2013 (I. Cerny)

[6] The TIRF REMS Assessment was evaluated in a separate OSE/DRISK Review DARRTS June 19, 2014 (I. Cerny) and is also part of ongoing negotiations/discussion between the DRISK TIRF REMS Assessment team and the TRIG.

- **On May 16, 2014,** an email information request was sent to the TRIG following internal discussions by the TIRF REMS Implementation Work Group that requested clarification from the TRIG on their proposal to add information in the Outpatient Pharmacy Overview document and FAQ about the TIRF REMS Cash Claim process (See Appendix C).
- **On May 30, 2014**, the TRIG responded to the Agency's May 16, 2014 information request and subsequent proposal to the TIRF REMS modification, which is discussed below in Sections 3 and 4. (See Appendix D)
- **On May 20, 2014,** the TRIG submitted to DMF 27320 Proposed TIRF REMS Modification #3, with proposed modifications to the TIRF REMS as previously discussed. All TIRF REMS Sponsors subsequently submitted prior approval supplement/Proposed REMS Modification letters referencing DMF 27320 between May 20 and May 21, 2014 (see Table 2 on Page 2 for detailed submission information). The proposed modifications as previously discussed above included the following:
    1. Revise REMS materials to eliminate product specific information (NDC numbers and reference to generics) which does not impact the safe use of TIRF Products
    2. Revise REMS materials to reference the currently approved TIRF products list on the FDA Approved REMS website rather than including throughout the REMS material as 'Attachment A'
    3. Revise the criteria in the REMS and REMS Supporting Document for triggers for inactivation of patient PPAF, including remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe
    4. Revise the REMS Supporting Document to include revised assessment metrics into the REMS Supporting Document, reviewed by the DRISK Assessment team under separate cover[7]
    5. Revise select Education Program material to emphasize and strengthen appropriate conversion and patient counseling information.
    6. Revise the pharmacy overview, FAQ documents, and select enrollment forms (independent and outpatient pharmacy enrollment forms), to add information about TIRF REMS Cash Claims in order to better clarify and define the TIRF REMS Cash Claim and required transaction process
    7. Revise the TIRF REMS Access website to incorporate items above and link respective Prescribing Information and MG to DailyMed

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions were reviewed for the proposed TIRF REMS modification:

[7] DRISK 18-Month REMS Assessment Report Review dated June 18, 2014. Reviewer: I. Cerny

- TIRF REMS Industry Group (TRIG) versus Drug Master File (DMF 27320) Transmucosal Immediate Release Fentanyl (TIRF) Access Program REMS Modification received May 20, 2014 (Seq. No. 009) and to individual applicant holders as per table below
- TIRF REMS Industry Group (TRIG) versus Accenture versus McKesson Specialty Health TIRF REMS Correspondence received May 30, 2014 (Seq. No. 010)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Cerny, I. DRISK Review of third (24 month, October 29, 2012 to October 28, 2013) Risk Evaluation and Mitigation Strategy (REMS) Consolidated Assessment Report for TIRF Agents dated June 19.
- Email communications between FDA/OSE and the TRIG, as identified above in Section 1.2 Regulatory History and appended to this review

3 PROPOSED REMS MODIFICATION WITH RATIONALE

3.1 REMOVAL OF NDC NUMBERS

The Agency proposed this modification to revise select REMS materials to eliminate product specific information (NDC numbers) and replace with a link on the TIRF REMS Access Program website that references the information for interested stakeholders. The TIRF Implementation Working Group determined that this revision will reduce burden on the Agency and TRIG for modifications to add or remove product NDC numbers.[8] Agreement was made that removal of this information and replacement with a link to this information that the TRIG will attest to keeping up to date will not impact the safe use of the TIRF products and minimizes the need for repeated modifications as the program continues to grow.[9] The impacted REMS materials include:

1. Independent Outpatient Pharmacy Enrollment Form
    a. Page 3 (deleted)
2. Chain Outpatient Pharmacy Enrollment Form
    a. Page 5 (deleted)
3. TIRF REMS Website Prototype
    a. See Section 3.8 below for details

Reviewer Comments: DRISK has reviewed the Sponsor's latest submission May 20, 2014, and we agree with this proposal to create a new document titled "TIRF

[8] TIRF Implementation Workgroup meets bi-weekly to discuss ongoing issues surrounding the TIRF REMS program. The workgroup is comprised of selected members from DRISK, DAAAP, Office of Compliance (OC), Office of Generic Drugs (OGD) and Office of Center Director (OCD)

[9] TRIG and FDA/OSE email communications dated February 5, 2014 and February 18, 2014 discussing proposed modifications (Section 1.2)

Products with NDC Numbers" which will be available as a PDF link on the TIRF REMS Access website Resources for Pharmacies and Resources for Distributors tabs.

However, we have additional recommendations.

1. The TRIG proposal included a hyperlink that referred stakeholders to the main www.TIRFREMSaccess.com site with additional directions to navigate through the Resources tabs to reach the appropriate web page that houses the 'TIRF Products with NDC numbers' pdf hyperlink. TRIG's proposed link to the main TIRF REMS Access Page with direction to navigate to specific tabs is not appropriate In an effort to minimize the need to navigate from the main page through multiple pages of the TIRFREMSaccess.com website required to reach the "TIRF Products with NDC numbers" pdf , please hyperlink directly to the pdf (i.e. www.TIRF REMSaccess.com/XXX).
2. The direct hyperlink to the pdf document "TIRF Products with NDC Numbers" pdf webpage should be included on the Independent outpatient pharmacy enrollment form and the Chain outpatient pharmacy enrollment form as indicated in our marked up track changes documents attached to this review. .
3. Submit a mock-up of the "TIRF Products with NDC Numbers" pdf document as part of the TIRF REMS Program Website Prototype.

Our full recommendations are provided in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.2 Removal of Reference to Generics

The Agency proposed this modification to revise select REMS materials to eliminate the reference to generics for specific products which does not impact the safe use of TIRF, and replace the reference to generics with (**) in the title of the table (i.e. Products ** Covered Under this Program), and an accompanying footnote stating "This includes approved generic equivalents of these products". As discussed above in Section 3.1, this revision originated from internal discussions about certain aspects of the TIRF REMS program that prompt repeated administrative process and modifications including the addition of generic drug names to select REMS material. Agreement was made that removal of this information and replacing with the referenced (**) and footnote did not impact the safe use of the TIRF products and minimizes the need for repeated modifications as the program continues to grow. Impacted REMS materials include:

1. Education Program for Prescribers and Pharmacists
    a. Page 17-19 table
    b. TIRF REMS Access Program Web Page 45-47

Reviewer Comments: DRISK has reviewed the Sponsor's latest submission dated May 20, 2014, and we agree with this proposal. Our full recommendations are provided in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.3 REMOVAL OF 'ATTACHMENT 1' LIST OF TIRF MEDICINES/REPLACE WITH HYPERLINK TO FDA APPROVED REMS WEBSITE

The Agency proposed this modification to remove 'Attachment 1' list of TIRF medicines in select REMS documents and replacing the list with a hyperlink that redirects the user to FDA Approved Risk Evaluation and Mitigation Strategy (REMS) website. As discussed above in Section 3.1, this revision originated from internal discussions about certain aspects of the TIRF REMS program that prompt repeated administrative process and modifications including the product list (Attachment 1/Table 1) which appears repetitively throughout select REMS material. Agreement was made that removal of this information did not impact the safe use of the TIRF products and minimizes the need for repeated modifications as the program continues to grow. The impacted REMS materials include:

1. TIRF REMS Document
    a. Page 3/f
    b. Page 8/c
    c. Page 9/c
    d. Page 11/c
    e. Page 16 III.
2. TIRF REMS Supporting Document
    a. Page 3-5
    b. Page 40-41
3. Overview for Prescribers
    a. Page 1
    b. Page 6
4. Prescriber Enrollment Form
    a. Page 1 (No. 6 attestation statement)
    b. Page 4 (deleted)
    c. TIRF REMS Access Program Web Page 71
5. Overview for Patients and Caregivers
    a. Page 1
    b. Page 3 (deleted)
6. Independent Outpatient Pharmacy Overview
    a. Page 1
    b. Page 7 (deleted)
7. Chain Outpatient Pharmacy Overview
    a. Page 1
    b. Page 7 (deleted)
8. Closed System Outpatient Pharmacy Overview
    a. Page 1
    b. Page 6 (deleted)
9. Independent Outpatient Pharmacy Enrollment Form

a. Page 1
b. Page 5 (deleted)
c. TIRF REMS Access Program Web Page 88-89

10. Chain Outpatient Pharmacy Enrollment Form
    a. Page 1 (No. 3 attestation statement)
    b. Page 6 (deleted)
    c. TIRF REMS Access Program Web Page 99-100
11. Closed System Outpatient Enrollment Form
    a. Page 1 (No. 3 attestation statement)
    b. Page 3 (deleted)
12. Inpatient Pharmacy Enrollment Form
    a. Page 1 (No. 3 attestation statement)
    b. Page 3 (deleted)
    c. TIRF REMS Access Program Web Page 80
13. Distributor Enrollment Form
    a. Page 1
    b. Page 3 (deleted)
14. TIRF Website Prototype and TIRF Website Landing Page
    a. See Section 3.8 below

Reviewer Comments: DRISK has reviewed the Sponsor's latest submission dated May 20, 2014, and we agree with the removal of Attachment 1 as previously discussed, throughout REMS and REMS appended material, in order to reduce redundancy throughout the material, however we have additional recommendations.

We agree that the information included on the FDA Approved REMS website (i.e. pharmaceutical manufacturer, contact information per product and NDA numbers) for TIRF products is beneficial for a select group of industry stakeholders, and therefore, a link to this information ("List of Application Numbers and Sponsors" at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM309784.pdf) should be provided in the REMS supporting document. Since it is relevant only to the Agency and TRIG members, it is appropriate for it to only be located in the REMS Supporting Document.

Since this information is less relevant for patients, providers and pharmacists and distributors, it is not necessary for this link to be included in the REMS appended materials. Therefore, we recommend including a link to the new webpage you created and submitted as Page 148 in the draft Website Prototype in the TIRF REMS document and appended materials wherever you have removed a reference to Attachment 1.

Furthermore, we recommend revising the table on Page 148 in the draft Website Prototype document as follows:

1. The table submitted should have only the column titles filled in. The remainder of the table should be blank.
2. Add the following attestation statement to Page 148 in the draft Website prototype document that reads: *The TRIG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website.*

Our full recommendations are provided in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.4 CRITERIA FOR INACTIVATION OF PATIENT-PRESCRIBER AGREEMENT FORM (PPAF)

The TRIF proposed a modification to revise the criteria for the description of triggers that will inactive a patient's PPAF, including the removal of the criteria of 'patients who receive prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame, that is suggestive of misuse, abuse, or addiction'. The modification also proposes the addition of criteria that will trigger inactivation of a patient PPAF. The current TIRF REMS has only one criteria listed which is "the patient has not filled a prescription for more than six (6) months. This revision proposes adding the following:

- PPAF has expired
- Patient is deceased
- Patient chooses to no longer participate in the TIRF REMS Access Program
- Substantive changes to the TIRF REMS Access Program

The impacted REMS materials include:

1. TIRF REMS Document
    a. Page 14/e
2. TIRF REMS Supporting Document
    a. Page 19

Reviewer Comments: The TRIG's proposed revisions to eliminate the trigger involving patient receipt of prescriptions from multiple prescribers were prompted by discussions during and subsequent to the DRISK review of the TIRF REMS 12-Month Assessment report[10], at which time agreement was reached to eliminate this criteria trigger due data provided by the TRIG that illustrated false positive results for this metric along with the added criteria that trigger inactivation listed above.[11] Given this information, we agree with this proposed revision.

The TRIG proposed the addition of the other criteria listed above, which would trigger the inactivation of a patient PPAF. We note that neither the 12-Month nor the 24-Month

[10] Cerny, I. TIRF REMS 12-Month REMS Assessment Review dated October 16, 2013.

[11] Jarral V. OSE communication to the TRIG including agreed upon triggers for inactivation of patient PPAF dated September 20, 2013.

TIRF REMS Assessment Report found any cases of patients being inactivated during the reporting period.[12] However, this reviewer finds it a feasible possibility the current specific criteria for patient inactivation may lack clarity and it is reasonable to propose added language to emphasize this information. And though we agree with the criteria added to include *PPAF has expired, Patient is deceased and Patient chooses to no longer participate in the TIRF REMS Access Program*, we do not agree with adding the criteria for when *Substantive changes to the TIRF REMS Access Program*. The TIRF REMS Access Program is a large and complex program with many moving parts. This criteria item is broad and ambiguous which could lead to confusion about what does and what does not constitute "substantive changes". Therefore, we recommend removing it from the proposed list of criteria. Our recommendations are provided in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.5 REVISION OF REMS ASSESSMENT METRICS

This modification proposes revisions to the select TIRF REMS Assessment Plan metrics. The impacted REMS materials include:

1. TIRF REMS Supporting Document
    a. Pages 29-34

Reviewer Comments: The TRIG's proposed revisions to the TIRF REMS Assessment plan that were included in the May 20, 2014 submission were based on numerous discussions between the TRIG and the TIRF REMS Assessment reviewer, along with subsequent discussions during bi-weekly TIRF REMS Implementation Workgroup meetings, which occurred between the time of the 24-Month Assessment report submission on December 27, 2013, and the TRIG's May 20, 2014 submission of the TIRF REMS Modification. We note that the DRISK TIRF REMS 24-Month Assessment review was not finalized at the time of the May 20 TIRF REMS Modification submission, therefore, internal negotiations regarding the TIRF REMS Assessment plan were still underway. Therefore, following the May 20, 2014 TIRF REMS modification submission, and in conjunction with complete of DRISK TIRF REMS 24-Month Assessment Review on June 18, 2014[13], additional modifications to the TIRF REMS Assessment plan were agreed upon and communication to the TRIG in the FDA August 21, 2014 REMS Assessment Acknowledgement/REMS Plan Revision communication to the TRIG.[14] Therefore, those revisions supersede revisions provided by the TRIG in the current TIRF REMS Modification submitted May 20, 2014.

Subsequently, as part of our comments to the TRIG for this TIRF REMS Modification review, we request a revision to the TIRF REMS Assessment Plan submitted with this

[12] TRIG 12-Month TIRF REMS Assessment Report, submitted December 20, 2012, and TRIG 24-Month TIRF REMS Assessment Report submitted December 27, 2013.

[13] Cerny, I. TIRF 24-Month Assessment Report Review dated June 18, 2014.

[14] DAAAP REMS Assessment Acknowledgement/REMS Plan Revision for TIRF REMS sent to the TRIG August 21, 2014.

proposed REMS modification to align with the August 21, 2014 REMS Assessment Acknowledgement/REMS Plan Revision communication sent by DAAAP. Additionally, we request revisions to the TIRF REMS Supporting Document that reflect updates to the audit plan, as reflect in the revised TIRF REMS Assessment Plan and acknowledged by the TRIG[15] where they cite regarding the addition of 4(b) - yearly audits of 5 inpatient pharmacies "The results of yearly inpatient audits will be included in 48-month report rather than the 36-month since a process does not yet exist in the TIRF REMS Access program for auditing inpatient pharmacies. The TRIG will need time to design a process to accomplish inpatient pharmacy audits; and, as a result, the inpatient pharmacy audit data will not be available in time for reporting in the 36-month assessment. Closed-system pharmacy audit information will, however, be available and be included in the 36-month report."

Our recommendations to include the revised TIRF REMS Assessment plan with additional information on the audit plan in the TIRF REMS Supporting Document are provided in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.6 REVISIONS TO ENHANCE KNOWLEDGE ABOUT CONVERSION OF TIRF MEDICINES

The TRIG states that they are proposing this modification to emphasize and strengthen risk messaging about the conversion of TIRF medicines based on prescriber survey and knowledge assessment results that demonstrated low comprehension of this concept.[16] The impacted REMS materials and proposed revisions include:

1. Education Program for Prescribers and Pharmacists
    a. Page 14 Appropriate Conversion - Bullet 1 '**bolded font'** as follows:

       TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

    b. Page 15 Appropriate Conversion – Bullet 2 '**bolded font'** as follows:

       Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.

    c. Page 20 Patient Counseling – Tell the Patient: Added statement as follows:

       Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients

[15] TRIG Email communication to OSE Project Manager Vaishali Jarral dated September 4, 2014.

[16] TRIG 24-Month REMS Assessment Report for Transmucosal Immediate-Release Fentanyl (TIRF) received December 27, 2013 (Seq. No. 0007)

d. TIRF REMS Access Web Pages 43 and 48 as revised above in a-c

Reviewer Comments: The TRIG proposes an emphasis on select language in the Education Program based on low comprehension of the concept. The TIRF REMS 24-Month Assessment Report Review found that in general, patients knowledge of key messages about key messages about 'not to switch TIRF medicines without medical input' were fairly high (88%+). Prescriber had a high level of understanding that TIRF medicines are not interchangeable with the exception of one subset question where prescribers scored less than 80%: prescribers scored 76% to the subset questions (12b) of Question 4 TIRF medicines are interchangeable with each other regardless of route of administration, which read "*The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose."* However, prescribers scored between 89%-98% on the other subset questions related to interchangeability of TIRF medicines. Similarly, pharmacy KAB survey results indicated a generally acceptable knowledge about interchangeability of TIRF medicines with 95% answering correctly 'false' that "*TIRF medicines are interchangeable with each other regardless of route of administration*" and similar results to related questions about interchangeability.[17]

DRISK believes that, although not a crucial deficiency finding of the TIRF REMS Assessment report, it is a reasonable proposal to strengthen select messaging to help enhance provider and patient knowledge and agree with this proposal with comments as indicated in below in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.7 INFORMATION ABOUT THE TIRF REMS CASH CLAIM TRANSACTION PROCESS

The TRIG proposed revisions to add information to select TIRF REMS material to enhance understanding about the correct TIRF REMS Cash Claim transaction process. The TRIG states that these revisions are proposed based on several pharmacies acknowledgement that they are unaware of the cash claim processing requirements, and is documented as part of the TIRF REMS 24-Month Assessment Report (Table 29, Non-Compliance Activity Reports by Stakeholders). The impacted REMS materials and proposed revisions include:

1. TIRF REMS Access Program Frequently Asked Questions (FAQ) Document
    a. Page 8 – Added text:

    Chain and Independent Outpatient Pharmacy CASH Claim FAQs

    What is the definition of a TIRF REMS CASH Claim?

    The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN

[17] Cerny, I. DRISK Review of third (24 month, October 29, 2012 to October 28, 2013) Risk Evaluation and Mitigation Strategy (REMS) Consolidated Assessment Report for TIRF Agents dated June 19.

using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?

Yes, all TIRF prescriptions, including CASH claims and other claims (i.e. workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?

Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program

2. Independent Outpatient Pharmacy Overview

    a. Page 5 – Step 2 Confirm prescriber enrollment. Proposed additions indicated below in **bold**:

    -Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. **This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).** Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
    -To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    ***Use BIN 014780 for all cash and non-third party claims.**

3. Chain Outpatient Pharmacy Overview

    a. Page 5/6 – Step 2 Confirm prescriber enrollment. Proposed additions indicated below in **bold**:

-Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. **This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).** Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.

-To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

- Patient First Name,
- Patient Last Name,
- Patient Date of Birth,
- Patient ZIP / Postal Zone,
- Quantity Dispensed,
- Days Supply,
- Prescriber ID,
- Prescriber Last Name

***Use BIN 014780 for all cash and non-third party claims.**

4. Closed System Outpatient Pharmacy Overview
    a. Page 4 – Step 2 Confirm prescriber enrollment. Proposed additions indicated below in **bold**:

- Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. **This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).**

Reviewer Comments: This proposal was submitted in preliminary communications between FDA and the TRIG, as outlined above in Regulatory History, prior to the formal May 20, 2014 submission of TIRF REMS Modification #3. On May 16, 2014, OSE sent an information request to the TRIG asking additional questions surrounding this proposed modification (see Appendix C). In response, the TRIG provided a response (see Appendix D) with additional details about the proposal, citing select results from the TIRF 24-Month REMS Assessment report, indicating non-compliance activities have occurred with cash transactions of TIRF product dispensing including seven (7) cases/pharmacies reporting not being aware of the cash claim process (utilizing the Cash BIN # when processing a TIRF prescription claim). In six out of seven of these cases, the pharmacist received a rejection but still dispensed the TIRF medicine, and in one case, the pharmacist did not submit a claim at all prior to dispensing the TIRF medicine. Based on our original May 16 inquiry, the TIRF reported that there have been an additional six non-compliance cases since the October 29, 2013 reporting period for the 24-Month

TIRF REMS Assessment. In all cases, the pharmacists reported not being aware of the requirement to process cash claims through the TIRF REMS Program or were aware of the cash claim procedure but received a rejection, yet dispensed the TIRF medicine anyway.

This information prompted internal TIRF REMS Workgroup discussions about this new awareness of an automation flaw for cash claim transactions for the TIRF REMS Program Switch System, used in pharmacies to communicate with the TIRF REMS Program to verify TIRF enrolment information prior to dispensing TIRF medicines. As discussions continue internally, and the challenges to any considerations that might remedy this issue at the individual pharmacy level, the workgroup agrees that added information, as proposed by the TRIG, may help provide education and awareness to pharmacies and pharmacists, about the correct cash claim transaction process. However, the group also believes that the addition of the following attestation to the Independent Outpatient and Chain Outpatient Pharmacy Enrollment Forms, will further enhance the dissemination of this important information:

> ***15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS access program without an insurance claim ((i.e. cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Program.***

Our full recommendations are provided in Section 5 along with accompanying Attachments that include DRISK comments and track change documents.

3.8 UPDATE THE TIRF REMS WEB PROTOTYPE DOCUMENT AND WEBSITE LANDING PAGE

This modification proposes revisions to the TIRF REMS Access Web Prototype and Website Landing Page, that incorporations all changes outlined above, where identified, along with the following additional revisions (See Appendix E 'TIRF Website Prototype Changes' for a complete list of website revisions):

1. Resources for Prescribers Tab – Page 142 Update Page as follows:
    a. To remove the PDF icons from MG and PI
    b. New PDF link for 'Product List for TIRF REMS Access Program'
    c. Combining US Prescribing Information and Medication Guide with hyperlink to DailyMed.
2. Resources for Patients Tab – Page 143 Update Page as follows:
    a. To remove the PDF icons from MG and PI
    b. New PDF link for 'Product List for TIRF REMS Access Program'
    c. Combining US Prescribing Information and Medication Guide with hyperlink to DailyMed.
3. Resources for Pharmacists Tab – Page 144 Update Page as follows
    a. To remove the PDF icons from MG and PI
    b. New PDF link for 'Product List for TIRF REMS Access Program'

c. New PDF link for 'NDC Listing for TIRF REMS Access Program'
d. Combining US Prescribing Information and Medication Guide with hyperlink to DailyMed.

4. Resources for Distributors Tab – Page 145 Update Page as follows:
    a. To remove the PDF icons from MG and PI
    b. New PDF link for 'Product List for TIRF REMS Access Program'
    c. New PDF link for 'NDC Listing for TIRF REMS Access Program'
    d. Combining US Prescribing Information and Medication Guide with hyperlink to DailyMed.
5. Product List - Page 148 Update Page as follows:
    a. Update the page to include 'Product List' to replace 'Attachment 1'

Reviewer Comments: DRISK has reviewed the Sponsor's latest submission dated May 20, 2014, for the proposed revisions to the REMS Web Prototype, including the website landing page, and other proposed modifications to REMS and appended material. We have provided our full recommended revisions in Section 5 along, with accompanying Attachments which includes DRISK comments and track change documents.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments below (Section 5: Comments for the Applicant) on the TIRF REMS Access Program REMS modification proposal be sent to the TRIG. Please request that the TRIG respond to these comments as soon as possible to facilitate further review for this submission.

The comments below are based on DRISK's preliminary review of the REMS modification proposal for TIRF products. Appended to this review is the REMS modification proposal and the REMS materials including comments and track changes (see Attachments 1 – 17).

5 COMMENTS FOR THE APPLICANT

We have the following comments, below, in response to your May 20, 2014 proposed TIRF REMS Modification submission, including redlined/track change documents (Attachments 1-17). Where indicated along with any redlined changes, FDA comments with recommendations in comment boxes in the documents or states FDA agrees with the proposed modification.

Your amendment submission must include the following documents:

1. Redlined, Word versions of all TIRF REMS materials which were revised during this modification
2. Clean, Word version of all TIRF REMS materials which were revised during this modification

3. One PDF of all final, clean TIRF REMS material (i.e. the TIRF REMS document and all TIRF REMS appended materials), except the TIRF REMS Supporting Document

5.1 General Comments

Throughout the REMS document as well as noted throughout all other REMS appended material, FDA notes the TRIG propose to remove the reference to Attachment 1 and replace is with a hyperlink to the FDA Approved REMS website. FDA agrees with the removal of Attachment 1 throughout the TIRF REMS appended material. FDA further agrees that linking to the FDA TIRF REMS list of products (including NDA numbers, manufacturers and contact information) may be helpful in the TIRF REMS Supporting document for TRIG Sponsors and FDA. However, we do not agree that linking to this FDA webpage would be helpful for other stakeholders (prescribers, patients, pharmacies and distributers). Therefore, FDA proposes instead:

1. All former references in REMS documents and REMS appended materials to the list of TIRF products on Attachment 1 should now provide a link to a new web page on the TIRF REMS Access website (Page 148 in the draft REMS Website Prototype) and **not link to the following FDA website:** http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

The following documents are affected:

- REMS Document (Attachment 1)
- An Overview for Prescribers (Attachment 2)
- Education Program for Prescribers and Pharmacists (Attachment 3)
- Prescriber Enrollment Form (Attachment 4)
- Overview For Patient and Caregiver (Attachment 5)
- Frequently Asked Questions (FAQ) (Attachment 6)
- Overview For Independent Outpatient Pharmacies (Attachment 7)
- Overview For Chain Outpatient Pharmacies (Attachment 8)
- Overview For Closed System Outpatient Pharmacies (Attachment 9)
- Overview For Inpatient Pharmacies (Attachment 10)
- Independent Outpatient Pharmacy Enrollment Form (Attachment 11)
- Chain Outpatient Pharmacy Enrollment Form (Attachment 12)
- Closed System Outpatient Pharm Enrollment Form (Attachment 13)
- Inpatient Pharmacy Enrollment Form (Attachment 14)
- Distributor Enrollment Form (Attachment 15)

2. Please also use this web page link (Page 148 in the TIRF REMS Access Website Prototype) whenever you reference the "Product List for TIRF REMS Access Program" or "Products Covered for TIRF REMS Access Program" on each Resource page (tabs) including the Resources for Prescribers tab, Resources for Patients tab, Resources for Pharmacists tab, and Resources for Distributors tab on the TIRF REMS Access website.

5.2 REMS DOCUMENT (ATTACHMENT 1)

1. Most recent modification date will need to be updated to reflect approval of this pending TIRF REMS modification
2. Under #3 TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions (Item e) the TRIG proposes a listing of criteria that will trigger the inactivation of the patient's PPAF. FDA agrees with all except the last criteria "Substantive changes to the TIRF REMS Access program". We believe this is too broad and ambiguous and that this could be a source of confusion. Therefore, we request this criteria item be removed.

5.3 FREQUENTLY ASKED QUESTIONS (FAQ) (ATTACHMENT 6)

1. FDA agrees with the proposed modifications, as included in the attached redlined document

5.4 INDEPENDENT OUTPATIENT PHARM ENROLLMENT FORM (ATTACHMENT 11)

1. Based on information provided in the TIRF REMS 24-Month Assessment report and subsequent discussions about pharmacy-level non-compliance with the TIRF REMS Cash Claim process, FDA believes that in addition to added information the TRIG proposes in the FAQ about the Cash Claim transaction process, pharmacy knowledge about this process can be further enhanced through an additional attestation statement, and requests that an added attestation (No. 15) be added as follows and as indicated on the attached redlined document:

   15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS access program without an insurance claim ((i.e. cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Program.

2. FDA agrees with your proposal to add a pdf document "NDC listing for TIRF REMS Access Program products" listing TIRF products with NDC numbers. However, in an effort to minimize the need to navigate from the main page through multiple other pages of the TIRFREMSaccess.com site website to reach the "NDC listing for TIRF REMS Access Program" pdf, we recommend hyperlinking directly to the pdf (i.e. www.TIRF REMSaccess.com/XXX). This PDF link should be listed on this form.

5.5 CHAIN OUTPATIENT PHARM ENROLLMENT FORM (ATTACHMENT 12)

1. Based on information provided in the TIRF REMS 24-Month Assessment report and subsequent discussions about pharmacy-level non-compliance with the TIRF REMS Cash Claim process, FDA believes that in addition to added information the TRIG proposes in the FAQ about the Cash Claim transaction process, pharmacy knowledge about this process can be further enhanced through an

additional attestation statement, and requests that an added attestation (No. 15) be added as follows and as indicated on the attached redlined document:

15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS access program without an insurance claim ((i.e. cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Program.

2. FDA agrees with your proposal to add a pdf document "NDC listing for TIRF REMS Access Program products" listing TIRF products with NDC numbers. However, in an effort to minimize the need to navigate from the main page through multiple other pages of the TIRFREMSaccess.com website to reach the "NDC listing for TIRF REMS Access Program" pdf, we recommend hyperlinking directly to the pdf (i.e. www.TIRF REMSaccess.com/XXX).

5.6 SUPPORTING DOCUMENT

1. Page 3: Background: See the recommendations above in Section 5.1, and included in the attached redlined document
2. Page 19: As stated above in Section 5, FDA agrees with all of the reasons to consider inactivation of a patient PPAF **except** "or substantive program changes". We believe this is too broad and ambiguous and that this could be a source of confusion. Therefore, we request this criteria item be removed.
3. Page 29: REMS Assessment Plan: The TIRF REMS Assessment Plan (AP) should be revised/updated to align with the Agency's August 21, 2014 REMS ASSESSMENT ACKNOWLEDGMENT/REMS ASSESSMENT PLAN REVISION communication to the TRIG and individual TIRF products application holders, including information the TRIG provided in your September 4, 2014 email communication to the FDA about yearly audits *"Additionally, within the appended revised AP, the FDA included the addition of 4(b) - yearly audits of 5 inpatient pharmacies…The results of yearly inpatient audits will be included in 48-month report rather than the 36-month since a process does not yet exist in the TIRF REMS Access program for auditing inpatient pharmacies. The TRIG will need time to design a process to accomplish inpatient pharmacy audits; and, as a result, the inpatient pharmacy audit data will not be available in time for reporting in the 36-month assessment. Closed-system pharmacy audit information will, however, be available and be included in the 36-month report."* Since this information supersedes the REMS Assessment Plan submitted in the TIRF REMS Modification dated May 20, 2014, please revise accordingly per above.

5.7 WEB PAGE PROTOTYPE (ATTACHMENT 17)

1. Page 9: See the recommendations above in Section 5, and included in the attached redlined document. Additionally, FDA agrees with your proposal to add a pdf

document "NDC listing for TIRF REMS Access Program products" listing TIRF products with NDC numbers. However, in an effort to minimize the need to navigate from the main page through multiple other pages of the TIRFREMSaccess.com website to reach the "NDC listing for TIRF REMS Access Program" pdf, we recommend hyperlinking directly to the pdf (i.e. www.TIRF REMSaccess.com/XXX).

2. This pdf link (www.tirfremsaccess.com/XXX) should be included on the following TIRF REMS forms:

    a. Independent outpatient pharmacy enrollment form

    b. Chain outpatient pharmacy enrollment form

3. Page 88: Based on information provided in the TIRF REMS 24-Month Assessment report and subsequent discussions about pharmacy-level non-compliance with the TIRF REMS Cash Claim process, please add the following Attestation to reflect and further emphasize the clarifying information in FAQ. - add Attestation:

    15. *I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS access program without an insurance claim (i.e. cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Program.*

4. Page 99: Based on information provided in the TIRF REMS 24-Month Assessment report and subsequent discussions about pharmacy-level non-compliance with the TIRF REMS Cash Claim process, please add the following Attestation to reflect and further emphasize the clarifying information in FAQ. - add Attestation:

    15. *I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS access program without an insurance claim ((i.e. cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Program.*

5. Page 144-145: FDA agrees with the TRIG's proposal to add a pdf document version listing TIRF products with NDC numbers for the TIRF REMS Access Program. However, in an effort to minimize the need to navigate from the main page through multiple other pages of the TIRFREMaccess.com website to reach the "NDC listing for TIRF REMS Access Program" pdf, we recommend hyperlinking directly to the pdf (i.e. www.TIRFREMSaccess.com/XXX). This PDF link should be placed in the following places:

    a) Resources for Pharmacists tab of the REMS website

    b) Resources for Distributors tabs of the REMS website

c) Independent outpatient pharmacy enrollment form

d) Chain outpatient pharmacy enrollment form

Please provide a mock-up of the pdf table listing the products and their NDC numbers as an attachment to the REMS Supporting document. This table, when included as an attachment to the REMS Supporting document, should be blank with the following attestation statement included: *The TRIG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website.*

6. Page 148: Landing Page Titled "Currently Approved TIRF REMS Products**". We agree with the format and content of this table. However, in order to prevent REMS modifications when new products are added or removed from the TIRF REMS Access Program, as part of the Webpage prototype document, this table should be blank with the following attestation statement included: *The TRIG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website.* On the live TIRF REMS Access Program website, however, the table should be filled in and the attestation statement should NOT be included. Refer to the ER/LA Opioid analgesics as an example here: http://www.er-la-opioidrems.com/IwgUI/rems/products.action along with the approved ER/LA REMS (Page 37) http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf for reference.

ATTACHMENTS: TIRF REMS and TIRF REMS Appended Materials

APPENDICES

Appendix A: OSE Email to TRIG dated February 5, 2014

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Wednesday, February 05, 2014 1:40 PM
To: Werre, Karla L
Cc: Liberatore, Mark; Jenkins, Darrell
Subject: TIRF SSS REMS modification- proposal

Hello Karla,

Please see the agency's proposal to TRIG below in regards to TIRF SSS REMS. Kindly acknowledge the receipt of this email and please send us your feedback within 45 days of the receipt of this email.

"*FDA would like to begin discussing potential modifications to the TIRF REMS documents. The purpose of this modification (Modification #3) is to eliminate some product specific information in the REMS materials which does not impact the safe use of these products.*

4. Remove NDC numbers from the TIRF REMS Pharmacy Enrollment Forms

The TRIG agreed to this revision during Modification2 negotiations. The TRIG agreed to provide a reference on the enrollment forms to a new page on the TIRF REMS Access Program website which will have a listing of the current NDC numbers. The list of current NDC numbers will be updated within 72 hours of a TRIG sponsor notifying the vendor of new NDC numbers.

5. Remove Attachment 1 from the TIRF REMS document and appended materials.

Instead, the REMS document and appended materials will include a reference to the list of currently approved TIRF products, which is located at on the FDA Approved Risk Evaluation and Mitigation Strategy (REMS) website (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm) .

In addition, the list of approved products will be available on the TIRF REMS Access Program website. The TRIG will submit as part of the TIRF REMS Website Protocol a page which will contain a Table listing of the currently approved TIRF REMS products, Sponsor Name, Contact phone number and link to product specific information for each product as well as the following statement:

The TRIG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website

Trade Name	*Company*	*Phone Number*	*Information Links*

6. *Table 1 in the Education Program*

Remove the reference to generics for individual products and replace with a footnote that all this table includes approved generic equivalents of the covered products.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Always 100 mcg.	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge and generic equivalents	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

*** This includes approved generic equivalents of these products*

Thank you,

Vaishali Jarral, M.S., M.B.A
Safety Regulatory Project Manager Office of Surveillance and Epidemiology Center for Drug Evaluation and Research Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 4472
Silver Spring, MD 20993

301.796.4248

Appendix B: TRIG February 18 email response to OSE February 8 email communication

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Tuesday, February 18, 2014 10:02 AM
To: Jarral, Vaishali
Cc: Liberatore, Mark; Amanda Bulkley; Laura Baloun; Siressa Sremba; Servello, Diane L; Werre, Karla L
Subject: RE: TIRF SSS REMS modification- proposal

Dear Vaishali,

Please see the TRIG's responses below in regards to the Modification #3 proposed by the Agency in its e-mail [February 5, 2014] on the TIRF SSS REMS.

The e-mail read: "*FDA would like to begin discussing potential modifications to the TIRF REMS documents. The purpose of this modification (Modification #3) is to eliminate some product specific information in the REMS materials which does not impact the safe use of these products.*

1. *Remove NDC numbers from the TIRF REMS Pharmacy Enrollment Forms*

   The TRIG agreed to this revision during Modification2 negotiations. The TRIG agreed to provide a reference on the enrollment forms to a new page on the TIRF REMS Access Program website which will have a listing of the current NDC numbers. The list of current NDC numbers will be updated within 72 hours of a TRIG sponsor notifying the vendor of new NDC numbers.

   TRIG RESPONSE to Item #1: Pursuant to its agreement during the Modification 2 negotiations, the TRIG again affirms its agreement to this proposal **except:** that it will update the current NDC numbers within 3 **working** days rather than 3 **calendar** days/72 hours after a TRIG sponsor notifies the vendor of the new/changes to the NDC numbers. This amount of time is needed to make the necessary modifications to the website.

2. *Remove Attachment 1 from the TIRF REMS document and appended materials.*

   Instead, the REMS document and appended materials will include a reference to the list of currently approved TIRF products, which is located at on the FDA Approved Risk Evaluation and Mitigation Strategy (REMS) website (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm).

   In addition, the list of approved products will be available on the TIRF REMS Access Program website. The TRIG will submit as part of the TIRF REMS Website Protocol a page which will contain a Table listing of the currently

approved TIRF REMS products, Sponsor Name, Contact phone number and link to product specific information for each product as well as the following statement:

The TRIG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website

Trade	*Compa*	*Phone*	*Information*

TRIG RESPONSE to Item #2: The TRIG agrees to remove Attachment 1 from the TIRF REMS document and appended materials (referred to as Attachment A above) and include a reference in the REMS document and its appended materials to the list of currently approved TIRF products which is located on the FDA Approved Risk Evaluation and Mitigation Strategy (REMS) website. As part of this change, the TRIG agrees to*:*

- Ensure that the list of approved products will also be available on the TIRF REMS Access Program website.

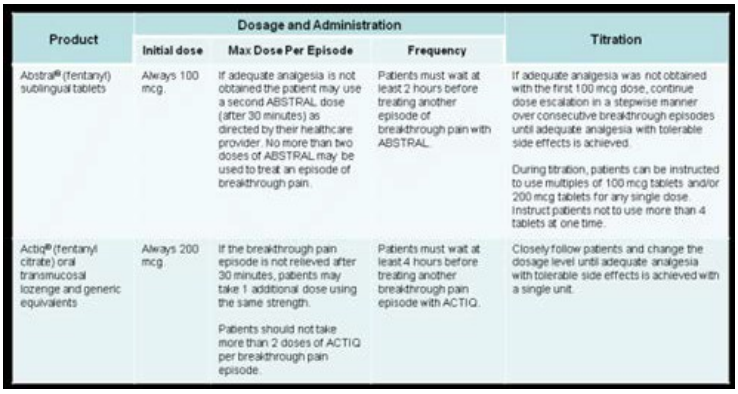
- The TRIG will submit as part of the TIRF REMS Website Protocol a page which will contain a Table listing the currently approved TIRF REMS products, Sponsor Name, Contact Phone Number and Information Links to product specific information for each product located on each TRIG Sponsors' company website(s) as well as the following statement:

    - The TRIG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website

3. *Table 1 in the Education Program*

Remove the reference to generics for individual products and replace with a footnote that all this table includes approved generic equivalents of the covered products.

Products** Covered Under this Program:



Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Always 100 mcg.	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge and generic equivalents	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Remove reference to generics

*** This includes approved generic equivalents of these products*

TRIG RESPONSE to Item #3: TRIG agrees to revise the product table in the Education program to remove the reference to generics for individual products and replace with a single footnote, "**This includes approved generic equivalents of these products."

IN ADDITION to the TRIG's responses to items listed above, the TRIG seeks the FDA's response on the following items:

- The TRIG inquires as to the FDA's expected timeline for approval of the TRIG's response to the assessment metrics submitted on January 31, 2014 by e-mail in documents entitled, "*Evaluation of the Metrics Outlined in FDA Document" and "Metrics to be Deleted/Not Included in FDA Document."* Analysis by the TRIG indicates that approval of the metric enhancements and their inclusion in Modification 3 would need to be received by March 31, 2014 in order to allow for system modification/enhancements and testing to facilitate inclusion of the new metrics in the 36-month assessment report.
- For Modification 3, the TRIG proposes removal of language from the REMS Supporting Document to deactivate patients shown to have multiple prescribers in an overlapping timeframe due to TRIG's concern for deactivating patients for non-compliance. TRIG has a limited view of data and is unable to confirm or rule out doctor-shopping because it may result in legitimate patient-access issues, particularly in view of the FDA's previous communication to TRIG during our teleconference meeting on November 14, 2013 that it should no longer report on doctor-shopping.
- TRIG is currently considering several program enhancements and will notify FDA within 45 days should TRIG decide to include them in Modification 3.

Kindest regards,
Karla
Karla Werre, MBA, RAC(US) | Manager, Regulatory Affairs
Specialty Generics | **Mallinckrodt Pharmaceuticals**
Mallinckrodt Inc.

Appendix C:

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]

Sent: Friday, May 16, 2014 7:28 AM

To: Werre, Karla L

Cc: Liberatore, Mark

Subject: TIRF REMS Modification #3 proposals

Hello Karla,

Reference is made to your April 15, 2014 response to our inquiry about your proposed "TRIG Recommendations for Programs Enhancements" sent March 24, related to the addition of information in TIRF REMS materials related to Cash Claim FAQs. In your response you clarified that per your 24-month assessment report Table 29 (page 72 of 131),7 instances of non-compliance occurred where TIRF medicines were dispensed without verifying stakeholder enrollment through the TIRF REMS pharmacy management system and that the pharmacies involved "were either not aware of the requirement to process cash claims through the TIRM REMS Program or were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway." Your response also stated that to address "apparent prescription processing knowledge deficit" the proposed Cash Claim FAQ information would be added to emphasize that "all claims, highlighting cash claims specifically, must be submitted to the TIRF REMS Access Program to verify the enrollment status of the stakeholders before dispensing a TIRF medicine to a patient and to clearly provide the proper BIN number for transmission of cash claims data."

Prior to the information you provided, our understanding of the TIRF REMS Switch system transmission process was that the transaction is adjudicated through the switch automatically, whether the transaction was an insurance or cash claim. It appears that this is not the case and that, in fact, the process involves additional manual steps at the pharmacy level to enter the Cash BIN # into the system in order for the transaction to be adjudicated. We are concerned that the switch system is not a failsafe process for adjudication of TIRF REMS safety verifications prior to dispensing the product.

We have the following information request (IR) for the TRIG, in response to the information you have provided:

1. Provide a proposal to mitigate this failure mode to assure the Switch System cannot be bypassed prior to dispensing of TIRF products. Describe any ways that participating pharmacies' systems can be modified in order to automatically:

    a. adjudicate of cash claims and eliminate the required pharmacist manual entry of a BIN # and/or

    b. prevent the dispensing of a prescription if the cash claim is not transmitted to the TIRF REMS Access program.

    c. To what extent have certified pharmacies implemented such automated systems?

2. Please explain the method used to identify the 7 cases/7 pharmacies reported in your 24-month REMS assessment. Is the method used to identify these cases comprehensive in identifying all such cases?

3. Since the 24-month REMS assessment, have you identified any additional cases?

4. Provide the root cause analysis of how these cases occurred along with the TRIG's proposed plan for future detection/identification of cases such as these.

5. In your proposed modified FAQ, you ask pharmacists to transmit TIRF REMS CASH claims to the TIRF REMS Access Program using the REMS CASH BIN

    014780. FDA has heard that pharmacies may be using other processes to transmit their TIRF REMS cash claims. Please confirm that these instructions will work in all pharmacies that participate in the REMS, and that they will not interfere with those pharmacies standard REMS operating procedures.

Please submit the response to DMF by May 27, 2014.

Thank you

Appendix D: TRIG May 30 submission response to May 16 OSE information request about the Cash Claim transaction process (eCTD Seq. No. 0010)

Information Request Response to 16MAY2014 FDA Correspondence

There were 7 instances of non-compliance identified in the 24-month Assessment that were classified as not aware of the requirement to process cash claims through the TIRF REMS Program or were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway. In 6 of the 7 cases, the pharmacists submitted a claim, received a reject, but still dispensed TIRF medicine. Only 1 case involved a pharmacist who did not submit a claim prior to dispensing a TIRF medicine.

1. Provide a proposal to mitigate this failure mode to assure the Switch System cannot be bypassed prior to dispensing of TIRF products. Describe any ways that participating pharmacies' systems can be modified in order to automatically:

1.a. Adjudicate of cash claims and eliminate the required pharmacist manual entry of a BIN #.

Pharmacies utilize different pharmacy software and some systems can be configured to automatically adjudicate cash claims while others may not. The REMS Cash BIN was established to allow pharmacies unable to configure their systems to automatically adjudicate cash claims to still participate in the TIRF REMS program and ensure patient access to TIRF medicines in all pharmacies that elect to participate in the program. The TIRF REMS program requires all enrolled pharmacies to enable their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards. This allows the TIRF REMS program to automatically intercept the claim via NDC level routing and subsequently interrogate the REMS database, via the Switch Provider, to validate the enrollment status of the prescriber, patient and pharmacy.

1.b. Prevent the dispensing of a prescription if the cash claim is not transmitted to the
TIRF REMS Access program.

When a pharmacy enrolls in the TIRF REMS Access program, the pharmacist attests that a TIRF medicine will not be dispensed without verifying through a pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program; additionally, that all TIRF medicines, regardless of the method of payment, are submitted and processed through the pharmacy management system.

If a prescription is not transmitted to the TIRF REMS Access program there is no way to notify the pharmacist they should not dispense.

1.c. To what extent have certified pharmacies implemented such automated systems?

The TIRF REMS program cannot determine the extent of pharmacies using automated systems. As stated above, pharmacies utilize different pharmacy software and some systems can be configured to automatically adjudicate cash

claims while others may not. The REMS Cash BIN was established to allow pharmacies unable to configure their systems to automatically adjudicate cash claims to still participate in the TIRF REMS program and ensure patient access to TIRF medicines in all pharmacies that elect to participate in the program.

2. **Please explain the method used to identify the 7 cases/7 pharmacies reported in your 24- month REMS assessment. Is the method used to identify these cases comprehensive in identifying all such cases?**

If a prescription is not transmitted to the TIRF REMS Access program there is no way to identify potential non-compliance. All 7 instances were reported by stakeholders, (6 pharmacies and 1 prescriber), via a phone call into the TIRF REMS Access program call center. All call center agents are trained to identify potential non-compliant events and triage them to the Non-Compliance Review Team for further review, investigation, and appropriate corrective action to mitigate future occurrences.

3. **Since the 24-month REMS assessment, have you identified any additional cases?**

Since the 24-month assessment data cut-off, (October 29, 2013), there have been 6 additional non-compliances cases that have been classified as not aware of the requirement to process cash claims through the TIRF REMS Program or were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway. In 4 of the 6 cases, the pharmacist submitted a claim, received a reject, but still dispensed TIRF medicine. Two cases involved a pharmacist who did not submit a claim prior to dispensing a TIRF medicine.

4. **Provide the root cause analysis of how these cases occurred along with the TRIG's proposed plan for future detection/identification of cases such as these.**

The root cause is the lack of clear messaging around the requirement for cash claim processing in TIRF REMS resources for pharmacists. As a result, the TRIG is proposing to modify TIRF REMS pharmacist resources to emphasize the importance of submitting cash claims to the TIRF REMS Access program.

5. **In your proposed modified FAQ, you ask pharmacists to transmit TIRF REMS CASH claims to the TIRF REMS Access Program using the REMS CASH BIN 014780. FDA has heard that pharmacies may be using other processes to transmit their TIRF REMS cash claims. Please confirm that these instructions will work in all pharmacies that participate in the REMS, and that**

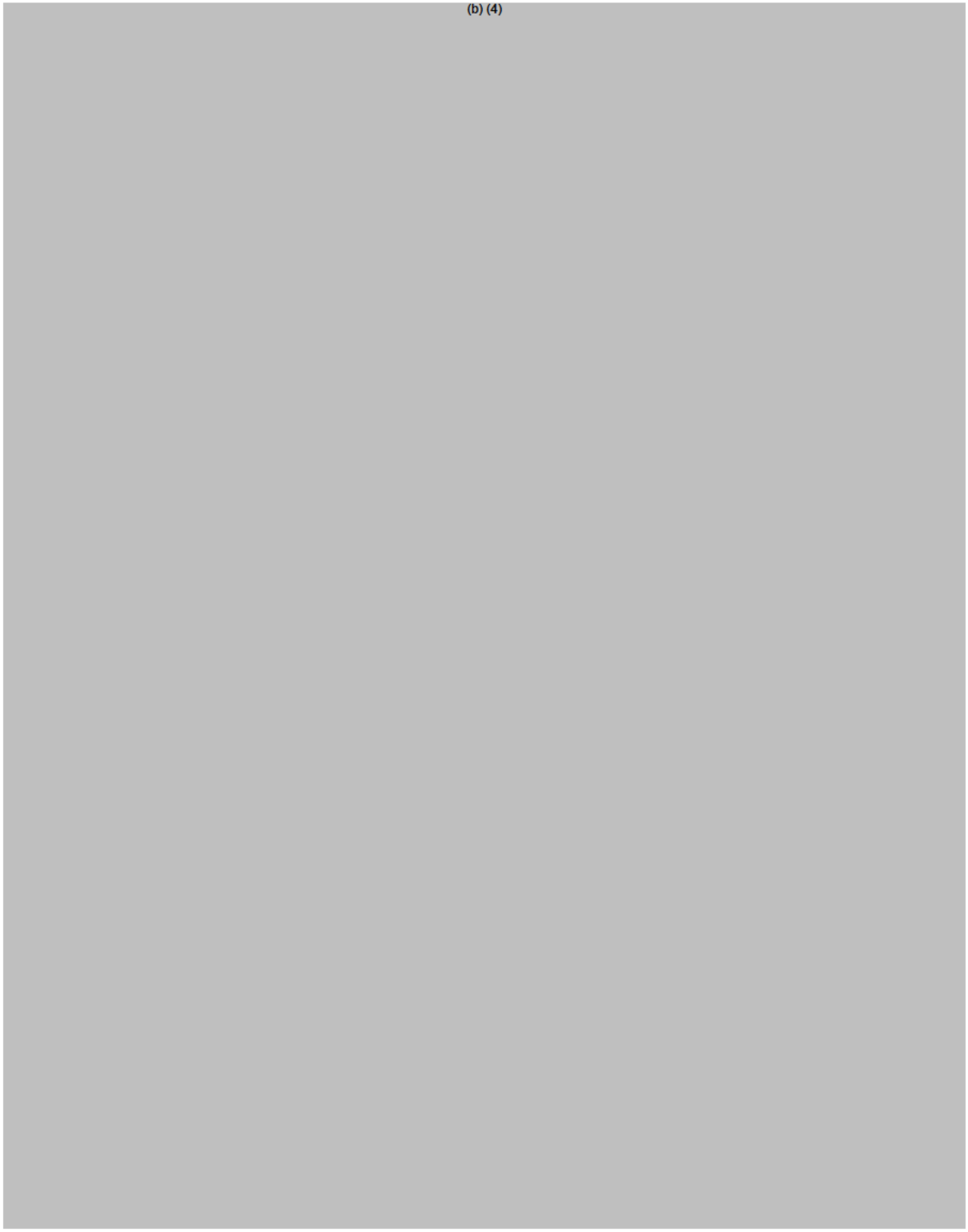
they will not interfere with those pharmacies standard REMS operating procedures.

The instructions in our proposed modified FAQs will work in all pharmacies that participate in the REMS. As stated above, the REMS Cash BIN was established to allow pharmacies unable to configure their systems to automatically adjudicate cash claims to still participate in the TIRF REMS program and ensure patient access to TIRF medicines in all pharmacies that elect to participate in the program.. Some pharmacies may use a different BIN for cash claims; however, the program intercepts the claim via NDC number, regardless of the BIN used, and subsequently interrogates the REMS database, via the Switch Provider, to validate the enrollment status of the prescriber, patient and pharmacy.

Appendix E: TIRF Website Prototype Changes

TIRF Website Prototype Changes

(b) (4)




(b) (4)

Initial REMS approval: 12/2011

Most recent modification: ~~XXXXXX~~11/2013~~XX~~/2014

Comment [A1]: Most recent modification date will be updated to reflect the final REMS modification approval date

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF)
RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Formatted: Numbered + Level: 1 + Numbering Style: I, II, III, ... + Start at: 1 + Alignment: Right + Aligned at: 0" + Indent at: 0.25"

FOLLOWING THIS PAGE, FDA_6738 TO FDA_6997 WITHHELD IN FULL AS B(4)/CCI (PROPOSED/DRAFT REMS WEB MATERIALS)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHY A MILLER
10/20/2014

KIMBERLY LEHRFELD
11/03/2014