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

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set # 1

Date:	February 1, 2013
Reviewers:	Kimberly Lehrfeld, Pharm.D., Risk Management Analyst Division of Risk Management
Team Leader:	Reema Mehta, Pharm.D., M.P.H. Division of Risk Management
Division Director:	Claudia Manzo, Pharm.D. Division of Risk Management
Drug Name(s):	See Table below
Therapeutic Class:	Opioid Agonist
Dosage and Route:	Transmucosal Immediate-Release Fentanyl (TIRF)

Drug Name	Dosage and Route	Application Type/Number	Supplement Number	Applicant/ Sponsor	TSI #
Abstral (fentanyl)	Sublingual tablet	NDA 22-510	S-007	Prostrakan, Inc.	290
Actiq (fentanyl citrate)	Oral transmucosal lozenge	NDA 20-747	S-037	Cephalon, Inc.	290
Fentora (fentanyl citrate)	Buccal tablet	NDA 21-947	S-017	Cephalon, Inc.	290
Lazanda (fentanyl)	Nasal spray	NDA 22-569	S-005	Archimedes Pharma US Inc.	290
Onsolis (fentanyl)	Buccal soluble film	NDA 22-266	S-012	Meda Pharmaceuticals	290
Subsys (fentanyl)	Sublingual spray	NDA 202-788	S-004	Insys Therapy	290

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1 INTRODUCTION

This is an interim review of the proposed modification of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) submitted by the Transmucosal REMS Industry Group sponsors (TRIG) between September 24 – 28, 2012 (See Section 2, Table 1)

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, and
- Approved generic equivalents of these products

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

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

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

The elements included in the program are Medication Guides 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:

A single shared REMS program, the TIRF REMS Access Program, was approved on December 28, 2011.

On June 30, 2012, the TIRF REMS was modified for the following reasons:

- Modification of the REMS document to allow participation of Closed System Pharmacies and inclusion of a closed system enrollment form.
- Addition of information about Subsys (fentanyl sublingual spray), whose REMS was newly approved on January 4, 2012, to pharmacy enrollment forms, DHCP letters, the education program, and Attachment 1 of the REMS.

On June 28, 2012, FDA requested a modification to the TIRF REMS to incorporate information about the closed system pharmacies into the appended REMS materials. The TRIG was sent the following request via email:

I. Create the following document:

1. *TIRF REMS Program Overview for Closed System Pharmacies*

II. Modify the following documents:

1. REMS Document

   Minor modification on page 11 to add the new Overview to the list

2. FAQ

   Add the following or a similar question: What if our pharmacy's management system cannot communicate with the TIRF REMS Access program (e.g. does not electronically transmit claims information)? You will need to contact the TIRF REMS Access program at 1-866-822-1483 to see if you qualify to enroll as a "closed system pharmacy".

3. *Website*

   Please provide feedback and/or a proposal as to what closed system pharmacy information and/or which documents will be posted on the TIRF REMS Website (we note your e-mail to Kimberly Compton on 6/22/2012 that stated that the enrollment form will not be posted, given that a pharmacy needs to be validated as being a closed system pharmacy prior to their enrollment). For example, closed-system pharmacies that are seeking to enroll in the TIRF REMS should understand that

there is a mechanism for them to participate in the REMS; however, it also needs to be clear this mechanism is not an option for pharmacies that can process through their pharmacy management system.

4. Supporting Document
    - Update to include information and a section on 'Closed System Pharmacies'
    - Update your REMS Assessment Plan and TIRF REMS Access Non-Compliance Plan

2 MATERIALS REVIEWED

Table 1: NDA submissions

Drug Name	Application Type & Number	FDA Received Date	Supplement Number
Abstral®	NDA 22-510	September 28, 2012	07
Actiq®	NDA 20-747	September 26, 2012	37
Fentora®	NDA 21-947	September 26, 2012	17
Lazanda®	NDA 22-569	September 28, 2012	5
Onsolis®	NDA 22-266	September 26, 2012	12
Subsys®	NDA 202-788	September 25, 2012	4

REMS documents included in these submissions:

- TIRF REMS document
- TIRF REMS Supporting document
- TIRF REMS Closed System Pharmacy Overview
- TIRF REMS Patient-Prescriber Agreement Form (PPAF)
- TIRF REMS Frequently Asked Questions (FAQs)

3 SUMMARY OF APPLICANT'S PROPOSED REMS MODIFICATION

3.1 REMS DOCUMENT AND REMS APPENDED MATERIALS

3.1.1 Closed System Pharmacy Overview Document

As requested by FDA, a reference to the Closed System Pharmacy Overview document was added to page 11. Additionally, a Closed System Pharmacy Overview document was added as an appended REMS material, which contains a similar format as the other overview documents contained within the program.

Reviewer Comment: Upon review, it was determined the Closed System Pharmacy Overview document could benefit from revisions to improve clarity and flow. As a result, the document was revised (see Attachment 11). Additionally, the Agency has

included a request for the TRIG to implement similar changes to the overview documents for the other stakeholders, as applicable.

3.1.2 Patient Prescriber Agreement Form (PPAF)

1. Removal of patient phone number as a mandatory field necessary for patient enrollment
   On August 30, 2012, the TRIG provided the Agency with the following request via email:

   > Some TIRF sponsors have received complaints from physicians indicating that the current requirement for the patient's phone number to be populated on the PPAF is affecting their practice of medicine.
   >
   > Because the patient phone number is not used by McKesson for anything specific at this point, the TRIG proposes removing it as a requirement for PPAF completion. As this is a minor change, McKesson is able to make the change to the system so that the phone number is not a required field and when the full REMS is ultimately filed to the DMF, the actual form will then be changed to delete the space for inputting the patient's phone number.

   Reviewer Comment: On September 20, 2012, an email was sent to the TRIG acknowledging the TRIG's intention to stop requiring a patient phone number in order to enroll patients. The form will be revised as part of this modification.

2. Changes in attestations in PPAF:

   In September 2012, the TRIG notified FDA they have received several complaints from TIRF-enrolled physicians that the attestation language in the PPAF regarding the requirement that a patient "is currently using around the clock opioid medication" and "is opioid tolerant" in order to be deemed eligible to use a TRIF medicine is restricting prescriber's use of medical judgment in the care of their patients.

   As of November 29, TRIG reported the following:

   - 4 prescribers have altered the PPAF to indicate their intention to prescribe to non-opioid tolerant patient and as a result these patients have not been allowed to enroll in the TIRF REMS Access Program or receive TIRF medicine.

   - 2 prescribers have written letters about cancer patient that had been on TIRF products without any around-the-clock opioids for at least 7 years, prior to the TIRF REMS implementation, and now do not have access to this medicine.

- TRIG has received informal feedback from other prescribers that indicate these concerns may be more widespread.

Reviewer Comment: DAAAP has also received informal feedback from physicians expressing the same sentiments that have been communicated by physicians to the TRIG sponsors. The TIRF REMS Implementation Team recommends the following revision to the PPAF to address the concern regarding patient access while maintaining the integrity of the program and protecting the safety of patients:

Prescriber Attestations:

1. ~~My patient is currently using around the clock opioid medication and has been for at least one (1) week.~~ I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. ~~My patient is opioid tolerant~~. I understand that p~~P~~atients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

Patient Attestations:

Removal of the following attestation:

~~I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.~~

Maintenance of this revised attestation:

I understand that if I stop taking ~~my~~ another opioid pain medicine that I have been taking regularly, around-the-clock, ~~opioid pain medicine~~ for my constant pain, then I must also stop taking my TIRF medicine.

The TIRF REMS Access Program still provides a consistent message and important restrictions that will adequately mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors. These revisions will decrease the impact of the REMS on the practice of medicine and allow patients who were appropriately treated prior to the implementation of the TIRF REMS Access Program to continue to receive TIRF medicines. Additionally, as a result of these revisions to the PPAF, the TIRF REMS document was edited to reflect the revised attestations.

3.1.3 Prescriber Enrollment Form

On July 20, 2012, the TRIG requested feedback from the FDA regarding the necessity of closed-system prescribers to enroll in the TIRF REMS Access program. The TRIG had that approximately 30-35 providers at the National Institutes of Health (NIH) were unable to register in the TIRF REMS because the prescribers at their institution do not have a DEA number, which is required to enroll in the TIRF REMS Access program. Some government closed system healthcare systems do not require prescribers to have an individual DEA number (i.e. NIH and Department of Defense).

Reviewer Comment: On July 30, 2012, FDA provided a response via email stating that all prescribers that are prescribing TIRF medications for outpatient use must enroll in the TIRF REMS Access program.

A teleconference was scheduled for August 9, 2012, to discuss these issues. The purpose of the teleconference was to discuss how the DEA number is currently used by the TRIG, and if the closed system prescribers have another unique identifier which can be used in the same way as the DEA number.

TRIG indicated that the DEA number is used for three purposes.

- to validate that the identity of the prescriber,
- to validate that a prescriber is eligible to prescribe schedule CII drugs, and
- to provide real time information to the pharmacy during the claims adjudication process that a prescriber is enrolled in the TIRF REMS Access program.

TRIG acknowledged that, since closed systems do not adjudicate claims, the National Provider Identifier (NPI) number could potentially be used in lieu of the DEA number for validation of these prescribers. An NPI number is unique to an individual prescriber, available online, and easy and free to obtain

Furthermore, the TRIG proposed a three step solution to address the problem.

- Enrollment: closed system prescribers can by-pass the need to populate the DEA field when enrolling by using a faxed form instead of the website. Therefore, the prescriber would only be required to provide their respective NPI number.
- Prescription verification via the call center: TRIG could modify the fields required for prescription verification to only include the NPI number for the prescriber when closed system pharmacies call the call center
- Validation of no individual DEA number: TRIG may require documentation from the closed systems that states their prescribers are not required to have individual DEA numbers in order to prescriber CII medications.

On September 27, 2012, the TRIG informed FDA via email that the TRIG approved the first 2 options above on September 18, 2012. On October 15, 2012, TRIG informed FDA the enrollment solution should be in place by November 15, 2012. The solutions proposed by the TRIG are acceptable by the FDA.

3.1.4 TIRF REMS Frequently Asked Questions (FAQ) document

As requested by FDA, the following language was added:

> *"What if our pharmacy's management system cannot communicate with the TIRF REMS Access program (e.g. does not electronically transmit claims information)? You will need to contact the TIRF REMS Access program at 1-866-822-1483 to see if you qualify to enroll as a "closed system pharmacy."*

3.1.5 Website Prototype

In response to the Agency's request for feedback and/or proposal for what closed system pharmacy information/documents should be posted on the TIRF REMS Website, the TRIG proposes:

1. On Page 165 "Resources for Pharmacies", the addition of a link to the Closed System Pharmacy Overview
2. On Page 167 "About the TIRF REMS Access Program", the inclusion of a new paragraph to educate closed-system pharmacies seeking to enroll in the TIRF REMS:

   "***Closed System Pharmacies*** *(e.g. integrated healthcare systems that dispense for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required) will not be eligible to purchase or dispense TIRF medicines unless an authorized pharmacist has reviewed the TIRF REMS Access Education Program and successfully completed the Knowledge Assessment and enrollment form. Enrolled pharmacies can only dispense prescriptions for TIRF medicines if the TIRF REMS Access program is contacted and authorization is received prior to the dispensing of a TIRF prescription."*

3. In addition to the requested additions to the Website, the TRIG notified the Agency of its intention to implement the following updates:
   - Page 18: Update Subsys NDCs on Terms and Conditions
   - Page 68: Education Slide – Update Subsys and Onsolis Trade Names
   - Page 92: Spelling correction #6 (labeled)
   - Page 101: Spelling correction #3 (labeled)
   - Page 109: Spelling correction #3 (labeled)
   - Page 110: Update Subsys NDCs on Terms and Conditions
   - Page 120: Spelling correction #3 (labeled)
   - Page 121 Update Subsys NDCs on Terms and Conditions
   - Page 132: Revised Language for PPAF in #12
   - Page 133: Remove PPAF Phone Number Requirement
   - Page 134: Revise Language for PPAF
   - Page 171: Replace with 'short – version' of Attachment 1

- Pages 90/99/107/118: Registration Complete – update language to provide appropriate next step
- Pages 92/101/109/120:Attestation- make the attestation requirement more prominent

3.1.6 Education Program

TRIG corrected Onsolis and Subsys product names on page 19, in the table.

3.1.7 Chain Pharmacy and Outpatient Pharmacy Enrollment Forms

The TRIG proposed the following edits:

1. Corrected the spelling of "labeled"
2. Capitalized medicine in the name of the document : 'List of TIRF Medicines Available only through the TIRF REMS Access program'
3. Added the Par Pharmaceutical NDC numbers 49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, and 49884-464-55 to the form's Terms & Conditions.

3.2 REMS SUPPORTING DOCUMENT:

As requested by FDA, the REMS Supporting Document was updated to add a specific section, "Closed System Pharmacies," as well as to include references and information pertaining to closed system pharmacies in the REMS Assessment Plan and TIRF REMS Access Non-Compliance Plan.

4 ADDITIONAL MODIFICATIONS PROPOSED BY THE AGENCY

4.1 REMS DOCUMENT

1. Clarification of the definition for wholesaler distributors

FDA received an inquiry from a third party logistics (3PL) provider regarding their need to enroll in the TIRF REMS program. The 3PL was informed by the TRIG that they needed to enroll in the TIRF REMS as a wholesale distributor. However, the 3PL expressed concern regarding their ability to comply with all of the REMS requirements (e.g., providing an EDI 867 transmission).

Therefore, DRISK and Office of Compliance met internally to assess the role of 3PLs in the drug supply chain and to assess the need to revise the TIRF REMS to better clarify the types of wholesaler distributors that must enroll in the program. The following criteria were identified to improve clarity regarding wholesaler distribution enrollment:

- Allow 3PLs who do not take title to or direct the sale or disposition of TIRFs to participate in the TIRF supply chain without enrolling in the REMS.
- Ensure that 3PLs who do take title to or direct the sale or disposition of TIRFs are enrolled in the REMS, and comply with the REMS requirements.

- Maintains the current restricted distribution channel for TIRFs without creating unnecessary barriers.

The proposed changes to the Implementation System in the REMS document include the addition of the underlined text below:

> TIRF Sponsors will ensure that wholesaler distributors who take title to or direct the sale or disposition of TIRF medicines to persons other than a consumer or patient are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. Clarification of types of Outpatient pharmacies

The current classification and nomenclature for pharmacies described in the approved TIRF REMS document is unclear. The REMS document states "Outpatient Pharmacies", "Chain Pharmacies" and "Closed System Pharmacies" dispense TIRF medicines for **outpatient** use. However, the current "Outpatient Pharmacy" category does not include Chain and Closed System pharmacies. Therefore, the current "outpatient pharmacy" category should be renamed "non-chain outpatient pharmacy" to clarify how it is distinct from the other pharmacies which dispense for outpatient use. In addition, the non-chain, chain and closed system pharmacies should be subcategories under the "Outpatient Pharmacies" category, since they all dispense for outpatient use and are required to verify the prescriber and patient are enrolled prior to dispensing TIRF medications. The "Inpatient Pharmacy" category should not be revised.

The 3 subcategories of outpatient pharmacies (non-chain, chain and closed system) should be clearly defined in the REMS document since they all have *different enrollment procedures*. First, there are different enrollment forms for each. In addition, the processes for enrolling additional closed system and chain pharmacy locations are different from each other and from how a unique non-chain pharmacy enrolls.
In summary, the TIRF REMS document should be revised to:

- Rename the current "outpatient pharmacy" category "Non-chain Outpatient Pharmacy."
- Re-organize by creating an "Outpatient Pharmacy" category with the following subcategories:
  - non-chain outpatient pharmacy,
  - chain outpatient pharmacy and
  - closed system outpatient pharmacy
- Define the subcategories of Outpatient Pharmacies that have different enrollment forms and processes

The majority of the proposed changes regarding outpatient pharmacies to the TIRF REMS document are in Section II.B.2. and are shown below. In addition, "outpatient pharmacy" was changed to "non-chain outpatient pharmacy" throughout the remainder of the document. See attachment 1 for all changes in the REMS document.

2. **TIRF medicines will only be dispensed by pharmacies that are specially certified.**

   a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

   b. Each pharmacy will be required to designate an authorized pharmacy representative (chain ~~pharmacy~~ and closed system pharmacies) or authorized pharmacist (~~outpatient~~ non-chain and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

   c. There are different ~~enrollment~~ requirements for :

   - **outpatient pharmacies** (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use)~~, including chain pharmacies, but excluding closed system pharmacies (see definition below).~~

      i. **chain pharmacy** Retail, mail order or institutional outpatient pharmacies that are part of 10 or more stores with the same ownership

      ii. **non-chain pharmacy** Retail, mail order, or institutional outpatient pharmacies that have less than 10 stores owned by a single entity

      iii. **closed system ~~pharmacies~~ pharmacy** For the purposes of this REMS, a closed system pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system pharmacies.

   - **inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

4.2 REMS APPENDED MATERIALS

The titles of the following REMS appended materials were revised as a result of the proposed clarifications to the REMS document described in Section 4.1:

Previous Title	**Proposed New Title**
Outpatient Pharmacy Enrollment Form	Non-Chain Outpatient Pharmacy Enrollment Form
Chain Pharmacy Enrollment Form	Chain Outpatient Pharmacy Enrollment Form
Closed System Pharmacy Enrollment Form	Closed System Outpatient Pharmacy Enrollment Form
Inpatient Pharmacy Enrollment Form	Inpatient Pharmacy Enrollment Form
Outpatient Pharmacy Overview Document	Non-Chain Outpatient Pharmacy Overview Document
Chain Pharmacy Overview Document	Chain Outpatient Pharmacy Overview Document

4.2.1 Patient Prescriber Agreement Form (PPAF):

Revision of Patient Privacy Notice statement on PPAF:

Upon review of the PPAF, it was noted that the patient privacy statement below implies the TIRF REMS Access program collects and reports to the FDA safety data including any "side effects" an enrolled patient experiences with a TIRF medication. However, the adverse event data reported for patients receiving TIRF medication is de-identified to protect the patient's identity. Therefore, in order to accurately reflect an enrolled patient's health information that is evaluated and reported to the FDA, the following revisions are proposed:

> ***I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to:***
>
> *a. Evaluate and report to the FDA about the proper use of TIRF medicines and the effectiveness of the TIRF REMS Access program.*
>
> ~~*b. Report to the FDA, about side effects from TIRF medicines and the TIRF REMS Access program effectiveness.*~~

4.2.2 Pharmacy and Prescriber Enrollment Forms

Addition of a field for Knowledge Assessment Authorization Number

Upon review of pharmacy and prescriber enrollment forms, it was noted that the form did not include a field for enrolled healthcare providers to indicate their Knowledge Assessment online training authorization number. The forms also do not provide instruction for submission of the Knowledge Assessment quiz if it was completed on paper. The following forms were revised to allow stakeholders to include this information on enrollment forms:

- Chain Outpatient Pharmacy Enrollment Form
- Non-Chain Outpatient Pharmacy Enrollment Form
- Closed System Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Prescriber Enrollment Form

4.2.3 Dear Healthcare Provider Letters (DHCP)

The TIRF REMS document states the DHCP letters should remain on the TIRF REMS Access Website for 1 year after approval on December 27, 2012. Therefore, the links to the DHCP letters can be removed from the website.

4.2.4 Frequently Asked Questions (FAQ) document

1. Revision of FAQ document as a result of the revisions to the REMS document described in Section 4.1.
2. Revision of text to reflect the completion of the transition phase from individual REMS programs to a single shared TIRF REMS program. After September 12, 2012, any pharmacy that has not agreed to the shared terms and conditions must re-enroll.

   When the TIRF REMS was approved on December 29, 2012, pharmacies which were enrolled in individual TIRF medication REMS programs were automatically transitioned into the single shared system TIRF REMS Access Program. In order to remain in the program and continue dispensing TIRF medicines, outpatient pharmacies had until September 12, 2012 to submit a signed shared terms and conditions document to the TIRF REMS Access Program. After that date, any pharmacy that had not complied would be inactivated and would be required to re-enroll in the TIRF REMS Access Program in order to dispense TIRF medications. In order to reflect this, the FAQ document has been revised as follows:

   > *"If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?"*
   >
   > All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access Program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access Program (see how to enroll below).
   >
   > You will be required to re-enroll in the shared TIRF REMS Access Program two (2) years after your last enrollment in an individual

REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

~~***Outpatient Pharmacy***~~

~~**Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.~~

~~Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not to agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.~~

~~You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.~~

~~The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.~~

~~Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.~~

~~You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.~~

~~***Chain Pharmacy***~~

~~**Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.~~

~~Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.~~

~~You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com~~

~~The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.~~

~~You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.~~

4.3 REMS SUPPORTING DOCUMENT

REMS Assessment Plan changes will be addressed in the current REMS Assessment which was submitted on December 21, 2012.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the TRIF REMS Access Program 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 following REMS materials including our track changes (see Attachment 1 – 12).

1. REMS Document
2. Non-Chain Outpatient Pharmacy Enrollment Form
3. Chain Outpatient Pharmacy Enrollment Form
4. Closed System Outpatient Pharmacy Enrollment Form
5. Inpatient Pharmacy Enrollment Form
6. Prescriber Enrollment Form
7. Frequently Asked Questions (FAQ)
8. Non-Chain Outpatient Pharmacy Overview
9. Chain Outpatient Pharmacy Overview

10. Closed System Outpatient Pharmacy Overview Document
11. Patient Prescriber Agreement Form
12. TIRF REMS Access Program Education Program
13. Website "Resources for Pharmacists" page 165
14. Website "Registration Identifier Question 2" pages 50-53

The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

6 COMMENTS FOR THE APPLICANT

6.1 REMS DOCUMENT

See Attachment 1 for redlined REMS document

1. Revision of REMS document to reflect the clarification of the types of outpatient pharmacies.

   The current classification of pharmacies described in the approved TIRF REMS should be revised to improve clarity. The current "outpatient pharmacy" category should be renamed "non-chain outpatient pharmacy" to clarify how it is distinct from the other pharmacies which dispense for outpatient use. In addition, the non-chain, chain and closed system pharmacies should be subcategories under the "Outpatient Pharmacies" category, since they all dispense for outpatient use and are required to verify the prescriber and patient are enrolled prior to dispensing TIRF medications. The "Inpatient Pharmacy" category should not be revised.

   The 3 subcategories of outpatient pharmacies (non-chain, chain and closed system) should be clearly defined in the REMS document since they all have *different enrollment procedures*.

   In summary, the TIRF REMS document should be revised to:

   - Rename the current "outpatient pharmacy" category "Non-chain Outpatient Pharmacy."
   - Re-organize by creating an "Outpatient Pharmacy" category with the following subcategories:
     - non-chain outpatient pharmacy,
     - chain outpatient pharmacy and
     - closed system outpatient pharmacy
   - Define the enrollment forms and procedures for the subcategories of Outpatient Pharmacies

   In addition, "outpatient pharmacy" was changed to "non-chain outpatient pharmacy" throughout the remainder of the document. See Attachment 1 for all changes in the REMS document.

2. Clarification of the definition for wholesaler distributor

   FDA received an inquiry from a third party logistics (3PL) provider regarding their need to enroll in the TIRF REMS program.

   FDA identified the following criteria to improve clarity regarding wholesaler distribution enrollment:

   - Allow 3PLs who do not take title to or direct the sale or disposition of TIRFs to participate in the TIRF supply chain without enrolling in the REMS.
   - Ensure that 3PLs who do take title to or direct the sale or disposition of TIRFs are enrolled in the REMS, and comply with the REMS requirements.
   - Maintains the current restricted distribution channel for TIRFs without creating unnecessary barriers.

   Therefore, revise the TIRF REMS to include the addition of the underlined text below:

   > II. C. 1. TIRF Sponsors will ensure that wholesaler distributors who take title to or direct the sale or disposition of TIRF medicines to persons other than a consumer or patient are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

3. Revision of Section II.B.1.b.ii.m. : Patient – Prescriber attestations to reflect changes described below in Section 6.2.5 Patient - Prescriber Agreement Form (see Attachment 11 for redlined version of the PPAF).

6.2 REMS APPENDED MATERIAL

6.2.1 TIRF REMS ACCESS Program Enrollment Forms

See Attachments 2 - 6 for redlined Enrollment forms

1. Revision of Titles of Enrollment Forms

   As a result of the above clarification in the REMS document, the titles of the following TIRF REMS Access program enrollment forms must be revised as indicated:

Previous Title	**Proposed New Title**
Outpatient Pharmacy Enrollment Form	Non-Chain Outpatient Pharmacy Enrollment Form
Chain Pharmacy Enrollment Form	Chain Outpatient Pharmacy Enrollment Form
Closed System Pharmacy Enrollment Form	Closed System Outpatient Pharmacy Enrollment Form

Inpatient Pharmacy Enrollment Form	Inpatient Pharmacy Enrollment Form

2. Addition of a field for Knowledge Assessment Authorization Number to Pharmacy and Prescriber Enrollment Forms

   The forms do not include a field for enrolled healthcare providers to indicate their Knowledge Assessment online training authorization number. The forms also do not provide instructions for submission of the Knowledge Assessment quiz if it was completed on paper. Update the following forms with this information.

   - Non-Chain Outpatient Pharmacy Enrollment Form
   - Chain Outpatient Pharmacy Enrollment Form
   - Closed System Outpatient Pharmacy Enrollment Form
   - Inpatient Pharmacy Enrollment Form
   - Prescriber Enrollment Form

6.2.2 TIRF REMS Access program Frequently Asked Questions (FAQ) document

See Attachment 7 for redlined FAQ document

1. Revision of FAQ document as a result of the revisions to the REMS document.

2. Revision of text to reflect the completion of the transition phase from individual REMS programs to a single shared TIRF REMS program. After September 12, 2012, any pharmacy that has not agreed to the shared terms and conditions must re-enroll.

In order to reflect the new terms of enrollment after September 12, 2012, the following FAQ question has been revised as indicated below:

> *"If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?"*
>
> All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access Program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access Program (see how to enroll below).
>
> You will be required to re-enroll in the shared TIRF REMS Access Program two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these

products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

6.2.3 Non-Chain and Chain Outpatient Pharmacy Overview

See Attachment 8 and 9 for redlined Outpatient Pharmacy Overviews

1. Revision of titles of Overview Documents

   As a result of the above clarification to the REMS document, the titles of the following TIRF REMS Access program Overview documents must be revised as indicated:.

Previous Title	**Proposed New Title**
Outpatient Pharmacy Overview Document	Non-Chain Outpatient Pharmacy Overview Document
Chain Pharmacy Overview Document	Chain Outpatient Pharmacy Overview Document

2. Revision of Non-Chain Outpatient Overview text to reflect the revisions in the REMS document to clarify types of outpatient pharmacies.

3. Revision of text to reflect after September 12, 2012 any pharmacy that has not agreed to the shared terms and conditions must re-enroll (see comment above regarding FAQs for details)

4. Revise the Non-Chain and Chain Outpatient Pharmacy Overviews to follow the same format as the revised Closed System Outpatient Pharmacy Overview document (See Attachment 10 for redlined Closed System Outpatient Pharmacy Overview)

6.2.4 Closed System Outpatient Pharmacy Overview

See Attachment 10 for redlined Closed System Outpatient Pharmacy Overview Document

1. The submitted Closed System Outpatient Pharmacy Overview has been revised to improve clarity and flow.
2. Revise the Non-Chain and Chain Outpatient Pharmacy Overviews to follow the same format as the revised Closed System Outpatient Pharmacy Overview document

6.2.5 Patient- Prescriber Agreement Form (PPAF)

See Attachment 11 for redlined PPAF

1. Revision of Patient Privacy Notice statement on PPAF

The patient privacy statement below implies the TIRF REMS Access program collects and reports to the FDA safety data including any "side effects" an enrolled patient experiences with a TIRF medication. However, the reported adverse event data is de-identified to protect the patient's identity. Therefore, in order to accurately reflect an enrolled patient's health information that is evaluated and reported to the FDA, the following revisions are proposed:

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to~~:~~

~~a. E~~valuate and report to the FDA about the proper use of TIRF medicines and the effectiveness of the TIRF REMS Access program.

~~b. Report to the FDA, about side effects from TIRF medicines and the TIRF REMS Access program effectiveness.~~

2. Removal of patient phone number as a requirement for patient enrollment

   Per FDA email sent September 20, 2012 acknowledging the TRIG's intention to stop requiring a patient phone number in order to enroll patients, the PPAF has been modified to remove the asterisk indicating this is a required field that must be completed for enrollment.

3. Revision of PPAF Attestations

   In September 2012, the TRIG notified FDA they have received several complaints from TIRF-enrolled physicians that the attestation language in the PPAF regarding the requirement that a patient "is currently using around the clock opioid medication" and "is opioid tolerant" in order to be deemed eligible to use a TRIF medicine is restricting prescriber's use of medical judgment in the care of their patients.

   FDA recommends the following revision to the PPAF to address the concern regarding patient access while maintaining the integrity of the program and protecting the safety of patients:

   Prescriber Attestations:

   1. ~~My patient is currently using around the clock opioid medication and has been for at least one (1) week.~~ I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.

   2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

   ~~3. My patient is opioid tolerant~~. I understand that p~~P~~atients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral

oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

Patient Attestations:

Removal of the following attestation:

~~I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.~~

Maintenance of this revised attestation:

I understand that if I stop taking ~~my~~ another opioid pain medicine that I have been taking regularly, around-the-clock, ~~opioid pain medicine~~ for my constant pain, then I must also stop taking my TIRF medicine.

6.2.6 Education Program

See Attachment 12 for redlined Education Program

Update Onsolis and Subsys on Slide 2 to align with TRIG's proposed revisions in the table on Slide 19: Products Covered Under this Program.

6.2.7 Dear Healthcare Provider Letters

Remove links to the DHCP letters from the website.

The TIRF REMS document states the DHCP letters should remain on the TIRF REMS Access Website for 1 year after approval on December 27, 2012. Therefore, the links to the DHCP letters can be removed from the website.

6.2.8 TIRF REMS Website

1. FDA acknowledges and accepts the TRIG's intention to implement the following updates to the Website:
   - Page 18: Update Subsys NDCs on Terms and Conditions
   - Page 68: Education Slide – Update Subsys and Onsolis Trade Names
   - Page 92: Spelling correction #6 (labeled)
   - Page 101: Spelling correction #3 (labeled)
   - Page 109: Spelling correction #3 (labeled)
   - Page 110: Update Subsys NDCs on Terms and Conditions
   - Page 120: Spelling correction #3 (labeled)
   - Page 121 Update Subsys NDCs on Terms and Conditions
   - Page 132: Revised Language for PPAF in #12
   - Page 133: Remove PPAF Phone Number Requirement
   - Page 134: Revise Language for PPAF
   - Page 171: Replace with 'short – version' of Attachment 1
   - Pages 90/99/107/118: Registration Complete – update language to provide appropriate next step

- Pages 92/101/109/120:Attestation-
  make the attestation requirement more prominent

2. Revisions to the following pages on the website:
   - "Resources for Pharmacists" page 165 of Website Protocol (See Attachment 13)
     - Links DHCP letters removed from page
     - Outpatient Pharmacy defined as including Non-Chain, Chain and Closed System Pharmacies.
     - Definition of types of pharmacies added to page
   - "Registration Identifier Question 2 –Pharmacy Staff" page 50-53 of Website Protocol

3. Update the website to reflect all revisions to the TIRF REMS Access Program materials.

6.3 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

6.4 GENERAL COMMENTS

1. Submit the form which will be used by Closed System Outpatient Pharmacies to validate prescriptions by completing and faxing to the TIRF REMS Access Program.
2. Submit the script used by TIRF REMS Access program call center staff when validating prescriptions for Closed System Outpatient Pharmacies.
3. What are the call center hours of operation?
4. Is validation of a Closed System Outpatient Pharmacy's TIRF prescription possible on weekends or on weekdays when the call center is not operational? Have there been any complaints from Closed System Outpatient Pharmacies due to them not being able to dispense TIRF prescriptions when the call center is not operational?
5. Currently Closed System Outpatient Pharmacies can only validate TIRF prescriptions via phone or fax. Are there plans to provide these pharmacies with an online interface for performing the validation?

Resubmission Instructions

1. Submit an amendment to the proposed TIRF REMS.
2. Include all of the REMS materials in the submission. For example, the REMS document, all materials that are appended to the REMS document (including the newly requested materials), and the REMS Supporting Document.
3. For any REMS materials that are being revised, provide both a clean and tracked changes version.

4. Submit all REMS materials in MS Word format.
    a. If certain documents, such as the REMS website are only in PDF format, they may be submitted as such. However, our preference is that as many materials as possible be provided in MS Word.

ATTACHMENTS:

1. REMS Document
2. Non-Chain Outpatient Pharmacy Enrollment Form
3. Chain Outpatient Pharmacy Enrollment Form
4. Closed System Outpatient Pharmacy Enrollment Form
5. Inpatient Pharmacy Enrollment Form
6. Prescriber Enrollment Form
7. Frequently Asked Questions (FAQ)
8. Non-Chain Outpatient Pharmacy Overview
9. Chain Outpatient Pharmacy Overview
10. Closed System Outpatient Pharmacy Overview Document
11. Patient Prescriber Agreement Form
12. TIRF REMS Access Program Education Program
13. Website "Resources for Pharmacists" page 165

FOLLOWING THIS PAGE, FDA_6421 TO FDA_6518 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/

KIMBERLY LEHRFELD
02/01/2013
TIRF REMS Single Shared System Interim Comments 1

REEMA J MEHTA
02/04/2013