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September 12, 2013

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

**Re: DMF #: 027320**
**Holder: McKesson Specialty Health (McKesson)**
**DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program**
**Re: REMS Shared Program**
**DMF Type: V**
**DMF Submission Information: Clinical/Clinical Information**
**REMS Submission Identifier: Assessment**
**eCTD Sequence Number: 0003**

Dear Drug Master File Staff:

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

As agreed upon during the Agency's teleconference held on July 31, 2013, the final historical document for the REMS Assessment 1 at 6 months would be submitted as a separate sequence (0003).

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

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

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

Sincerely,

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

Attachments: Table of Contents for the submission
Electronic Submission Specifications

**Assessment – 6 Month**

| Module Section | Description |
|---|---|
| 1.2 Cover Letter | Cover Letter w/ Attachments |
| 1.16 – Risk Management Plans | REMS History<br><br>REMS Assessment – 6 Month |

# Electronic Submission Specifications

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

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

| | |
|---|---|
| **Anti-Virus Program** | Symantec Endpoint Protection Edition |
| **Program Version** | 11.0.5002.333 |
| **Virus Definition Date** | 09/04/2013 rev. 3 |
| **Submission Size** | Approx. 1 MB |

The IT point of contact for this submission is:

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

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

**Document Number:** Version 1.0 FINAL

**Product Name:** Transmucosal Immediate Release Fentanyl

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

Archimedes Pharma US Inc.
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceuticals)
Insys Therapeutics Inc.
Meda Pharmaceuticals
Mallinckrodt Inc. (a Covidien Company)
Par Pharmaceutical, Inc.
ProStrakan, Inc.

**Confidentiality Statement**

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| | |
|---|---|
| AAPCC | American Association of Poison Control Centers |
| AERS | Adverse Event Reporting System |
| BTP | Breakthrough Pain |
| CSR | Center Service Representative |
| DEA | Drug Enforcement Administration |
| ETASU | Elements to Assure Safe Use |
| FDA | Food and Drug Administration |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| NCPDP | National Council for Prescription Drug Program |
| NDC | National Drug Code |
| NPI | National Provider Identifier |
| NRCT | Non-Compliance Review Team |
| PMS | Pharmacy Management System |
| PPAF | Patient-Prescriber Agreement Form |
| REMS | Risk Evaluation and Mitigation Strategy |
| REMS edits | Pass all checks to confirm that TIRF REMS Access program requirements were met. |
| SOP | Standard Operating Procedure |
| SOW | Scope of Work |
| TIRF | Transmucosal Immediate Release Fentanyl |
| TIRF Medicines | Transmucosal Immediate Release Fentanyl product(s) |
| TIRF REMS Access | REMS program for TIRF medicines |
| TIRF Sponsors | The group of sponsors that are submitting this REMS |
| TRIG | TIRF REMS Industry Group |
| UBC | United BioSource Corporation |
| US | United States |

## EXECUTIVE SUMMARY

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation Mitigation Strategy (REMS) Access program was approved by the Food and Drug Administration (FDA) on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS® and generic versions of these TIRF medicines. On 04 January 2012, the FDA approved the inclusion of SUBSYS™ to the TIRF REMS Access program. The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval.

Prior to the launch of the TIRF REMS Access program, 5,855 letters of notification were sent to Pharmacies and Prescribers already enrolled in an individual TIRF REMS program and 83,390 Dear Healthcare Professional letters were mailed to targeted prescribers and outpatient and inpatient pharmacies. Of these mailings, a total of 338 letters or e-mails were returned.

As of 12 March 2012, records for patients, prescribers, pharmacies, and distributors actively enrolled in independent TIRF REMS programs (i.e., enrollments were completed) were transitioned into the TIRF REMS Access program. Combined stakeholder enrollment (new and transitioned) in the TIRF REMS Access program during the current reporting period included 6,747 prescribers, 35,407 outpatient pharmacies, and 42 wholesaler/distributors. Additionally, 7,783 patients were enrolled who had prescription activity during the current reporting period.

Implementation of the TIRF REMS Access program for closed system pharmacies (integrated healthcare systems with outpatient pharmacy management systems [PMS] unable to support the electronic transmission for required validation and claims), has been deferred to 30 June 2012. Therefore, this assessment report does not include data from the closed system pharmacies.

No patients, inpatient or outpatient pharmacies, or wholesaler/distributor enrollments were inactivated during the reporting period. A total of 199 prescribers were inactivated with 98.0% due to expiration of enrollment period.

Among 2,423 newly enrolled prescribers who attempted and completed the knowledge assessments most prescribers passed the knowledge assessments on the first (43.5%) or second attempt (32.9%). Of the 2,183 enrolled authorized pharmacies, the majority completed the knowledge assessments on the first (37.6%) or the second attempt (38.8%).

There were 60 incomplete prescriber enrollment forms received (multiple forms may have been submitted for the same prescriber). The majority of incomplete forms were incomplete due to missing physician signature date (66.7%), missing signature (66.7%), and missing e-mail (33.3%).

There were 75 incomplete pharmacy enrollments attempts via Web, mostly due to missing Drug Enforcement Administration (DEA) number (16.0%), invalid DEA (13.3%), missing National Provider Identifier (NPI; 9.3%), and invalid NPI (6.7%). There were no incomplete forms received from wholesalers/distributors. A total of 5,799 patient-prescriber agreement forms (PPAFs) were submitted to the REMS program; the majority was submitted via the Web.

At total of 14,175 prescriptions were authorized and 94.3% of those authorized prescriptions were adjudicated for safety and approved for dispensing. No patient had more than 3 prescribers in a 6 month period.

A total of 8,668 prescriptions were dispensed to 7,148 patients during the first 10 days after patient enrollment (i.e., enrollment occurred when first prescription was filled). There were a greater number of patients who had their first prescription filled in the first 10 days without a PPAF compared with those patients with a PPAF (83.0% vs. 9.0%). For patients without a PPAF, the majority of patients (83.0%) received only 1 fill.

Of 2,188 outpatient pharmacies that attempted to configure a PMS, 96.3% successfully reconfigured their systems in a mean of 0.9 days to configure (min/max; 0.0001 days/42 days).

A total of 11,808 prescription claims were rejected for safety reasons (meaning the transaction failed to meet REMS requirements for prescriber and/or patient and/or pharmacy). A single prescription may have been submitted and rejected multiple times. The majority of safety reasons were due to prescriber ID not in the TIRF REMS Access database (46.8%), PPAF incomplete (23.6%), pharmacy not enrolled (17.9%), patient zip code missing from claim (14.5%), or prescriber last name did not match name registered (10.0%).

The TIRF REMS Access Call Center was contacted most frequently for the following reasons: enrollment status inquiry (18.7%), claim rejection due to pharmacy REMS edit (12.4%), claim rejection due to prescriber REMS edit (10.7%), PPAF inquiry (8.8%), and PPAF follow up (7.9%).

There were no reports from patients of inability to find an enrolled pharmacy. One prescriber reported that his/her local pharmacies were not enrolled; however, TIRF REMS Access program records showed that there were enrolled pharmacies in the area. There were no reports from patients of an inability to find an enrolled prescriber. No reports of inadvertent enrollment deactivations were identified; 10 reports concerning confirmed or potential non-compliant activity; and 5 issues were identified as system errors.

During the current reporting period, no FDA Adverse Event Reporting System (AERS) cases were reported. There were 9 cases of known exposure to oral fentanyl immediate-release medicines and 8 cases of exposure to unknown fentanyl reported to the American Association of Poison Control Centers (AAPCC) during the current reporting period. One death was reported in an unknown fentanyl case (indirect report). There were 3 pediatric exposures reported for TIRF medicines, including one minor effect, one moderate effect, and one no follow-up/non toxic effect.

Over all, the TIRF REMS Access program has adequately addressed its goals for the current reporting period.

# 1 BACKGROUND

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

Opioids are formulated as both extended release and immediate release products. Extended release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. Fentanyl, an opioid agonist and a Schedule II controlled substance, is approximately 100-fold more potent than morphine as an analgesic.[1] Secondary effects of fentanyl on central nervous system, respiratory and gastrointestinal functions are typical of opioid analgesics and are considered to be an effect.[2]

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

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

The FDA has determined that a REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access program was approved by the FDA on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS® and generic versions of these TIRF medicines. On 04 January 2012, the FDA approved the inclusion of SUBSYS™ to the TIRF REMS. The group of Sponsors that are submitting this REMS (Archimedes Pharma US Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceuticals], Insys Therapeutics Inc., Meda Pharmaceuticals, Mallinckrodt Inc. [a Covidien Company], Par Pharmaceutical, Inc., and ProStrakan, Inc.) are hereafter referred to as the TIRF Sponsors. The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. This report is prepared by United BioSource Corporation (UBC).

[1] Biedrzycki OJ, Bevan D, Lucas S, Fatal overdose due to prescription fentanyl patches in a patient with sickle cell/beta- thalassemia and acute chest syndrome: A case report and review of the literature. *Am J Forensic Med Pathol*. 2009 Jun; 30(2): 188-90

[2] Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007 Apr; 29(4):588-601.

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

**Table 1: TIRF Medicines**

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

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

## 1.1 Reporting Period

The initial REMS was approved on 28 December 2011 and went live on 12 March 2012. FDA requires an initial report 6 months after initial approval. For this reporting period the cut-off date was 27 April 2012 thereby allowing 60 days to prepare the report for the FDA, which is due on 28 June 2012.

Data cutoffs include all data/information available from the start of the reporting period up to the end of each reporting period to allow for programming, analysis, and report writing. Reports are scheduled for completion according to the following schedule:

| Reports | Reporting Interval | Date Sent to FDA |
|---|---|---|
| **6 months REMS Assessment** | 12/28/2011 - 04/27/2012 | 06/28/2012 |
| **12 months REMS Assessment** | 04/28/2012 - 10/28/2012 | 12/28/2012 |
| **24 months REMS Assessment*** | 10/29/2012 - 10/28/2013 | 12/28/2013 |

***Annually thereafter**

# 2 REMS 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.

## 2.1 The TIRF REMS Access Program Transition Plan: From Individual to Shared REMS

Upon launch of the TIRF REMS Access program on 12 March 2012, all stakeholders enrolled in an individual TIRF REMS program were transitioned to the TIRF REMS Access program. From this point onward, all new stakeholders will be required to enroll in the TIRF REMS Access program.

All distributors, pharmacies, and prescribers already enrolled in an individual TIRF REMS program were sent by mail the TIRF REMS Access program Distributor Letter, Pharmacy Letter or Dear Healthcare Provider Letter, respectively. Web sites, Call Centers, and enrollment forms for individual TIRF REMS programs were redirected to the TIRF REMS Access program.

Historical data from all individual TIRF REMS programs was referenced to determine the date of last prescription so that the TIRF REMS Access program could accurately calculate 6 months of prescription activity for each patient. Prescribers, inpatient and outpatient pharmacies, and distributors are required to re-enroll and successfully complete the enrollment requirements of the TIRF REMS Access program every 2 years from their last enrollment in the individual TIRF REMS program.

Independent TIRF REMS program bridging reports for individual TIRF REMS programs will capture the transitioned data (prior to launch of TIRF REMS Access program on 12 March 2012).

### 2.1.1 Prescribers

Enrollment data for each enrolled prescriber were transferred from the individual TIRF REMS program to the TIRF REMS Access program database. After this transfer, these prescribers were then able to prescribe any TIRF medicine within the TIRF REMS Access program.

Healthcare providers were guided to review the educational program for the TIRF REMS Access program but were not tested on these materials.

### 2.1.2 Inpatient Pharmacies

Enrollment data for each enrolled inpatient pharmacy were automatically transferred from the individual TIRF REMS program to the TIRF REMS Access program database. After this transfer, inpatient pharmacies were then able to order and dispense any TIRF medicine within the TIRF REMS Access program to inpatients.

### 2.1.3 Outpatient Pharmacies

Enrollment data on all outpatient pharmacies in an individual TIRF REMS program were automatically transitioned to the new TIRF REMS Access program.

However, chain pharmacies were required to execute a TIRF REMS Access program contract with their switch provider before they could order and dispense all TIRF medicines. (A switch provider provides information to pharmacists at point-of-dispensing via their pharmacy terminals. Their secure connectivity network provides a single point of access between pharmacies and the TIRF REMS Access program so that transactions are routed through the program for evaluation of the eligibility rules.) Chain pharmacies that had not executed a TIRF REMS Access program contract with their switch provider were still able to dispense those TIRF medicines with an individual TIRF REMS program(s), in which they previously enrolled, for up to 6 months from 12 March 2012 (launch of the TIRF REMS Access program). If chain pharmacies do not execute a TIRF REMS Access program contract with their switch provider within six months, they will no longer be able to order or dispense any TIRF medicine.

Independent pharmacies must agree to the shared program terms and conditions before they could order and dispense all TIRF medicines. Independent pharmacies that had not agreed to the shared program terms and conditions were still able to dispense those TIRF medicines with an individual TIRF REMS program(s), in which they previously enrolled, for up to 6 months from availability of the TIRF REMS Access program. If independent pharmacies do not sign the new terms and conditions within six months, they will no longer be able to order or dispense any TIRF medicine.

### 2.1.4 Patients

Enrollment data for patients were automatically transferred from the individual TIRF REMS program to the TIRF REMS Access program database. Patients who were enrolled in an individual TIRF REMS and had completed a PPAF could be prescribed/receive any TIRF medicine within the TIRF REMS Access program. Patients are only required to complete a new PPAF for the TIRF REMS Access program every 2 years from the date of their last PPAF submission.

### 2.1.5 Distributors

Enrollment data for distributors were transferred from the individual TIRF REMS programs to the TIRF REMS Access program database.

## 3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

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

Provisions were made to transition stakeholders from individual TIRF REMS programs into the TIRF REMS Access program (see Section 2.1). Program materials are provided on the TIRF medicines in addition to product-specific materials. The Educational Program and Knowledge Assessment components of the program contain both TIRF medicine class and product-specific components. All program tools, including enrollment forms, PPAF, stakeholder letters, and overview documents containing program information specific to the TIRF REMS Access program, are available through the www.TIRFREMSACCESS.com Web site.

The program procedures are monitored for adherence and were modified as necessary to ensure optimal effectiveness (see Section 5.4, System Error #5). The TIRF Sponsors will continue to conduct ongoing and retrospective analysis as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

### 3.1 Additional Elements

#### 3.1.1 Medication Guide

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

#### 3.1.2 Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS was not required. However, TIRF Sponsors sent materials to targeted stakeholders to support implementation of the TIRF REMS Access program. These communications included Dear Healthcare Provider and Dear Pharmacy letters, and informed prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access program and means of reporting adverse events.

The target audience for the Dear Healthcare Provider letter included pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians and primary care physicians), oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines.

Separate Dear Pharmacy Letters were sent to inpatient pharmacies and outpatient pharmacies. The target audience for the letter included outpatient and inpatient pharmacies that may be involved in dispensing TIRF medicines.

### 3.2 Elements to Assure Safe Use (ETASU)

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

TIRF medicines are only to be available through the TIRF REMS Access program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines were only dispensed to appropriate patients, pharmacies are enrolled into the TIRF REMS Access program. There was a different set of enrollment requirements for outpatient pharmacies (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and inpatient pharmacies (e.g. hospitals that dispense for inpatient use only). For Long-Term Care and Hospice patients whose prescriptions were obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber were enrolled in the TIRF REMS Access program.

Implementation of the TIRF REMS Access program for closed system pharmacies, which are 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, has been deferred to 30 June 2012. Therefore, this assessment report does not include data from the closed system pharmacies.

Outpatient pharmacy enrollment required an authorized pharmacist at the pharmacy to undergo enrollment through review of the TIRF REMS Access Education Program and successful completion of the Knowledge Assessment on behalf of the pharmacy and submission of a completed and signed TIRF REMS Access program enrollment form. The authorized pharmacist ensured the pharmacy enabled their pharmacy management system (PMS) to support communication with the TIRF REMS Access program using established telecommunication standards. This required standardized validation test transactions to validate the system enhancements. The authorized pharmacist was responsible for educating all pharmacy staff who participated in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training was documented and subject to audit.

For inpatient pharmacy enrollment, the authorized pharmacist underwent the TIRF REMS Access Education Program, successfully completed the Knowledge Assessment, and submitted a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist acknowledged that they understood that outpatient pharmacies within their facility were to be separately enrolled.

For chain pharmacies, an authorized chain pharmacy representative completed enrollment. The authorized chain pharmacy representative acknowledged that training would occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment were completed, the authorized chain pharmacy representative, on behalf of the chain, was required to acknowledge their understanding of the appropriate use of TIRF medicines and to agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form.

Patients were enrolled in the TIRF REMS Access program when their first prescription was processed at the pharmacy. A completed PPAF needed to be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of three prescriptions were allowed within 10 working days from when the patient had their first prescription filled. No further prescriptions were dispensed after the 10 working day window until a completed PPAF was received. A patient's healthcare provider can submit a copy of the PPAF to the TIRF REMS Access program via the Web site, fax, or US mail. Data regarding the receipt of PPAFs from individual TIRF REMS programs were transitioned into the TIRF REMS Access program (see Section 2.1.4). In some cases, a PPAF may never be received if the patient received only one prescription without a PPAF and never attempted to fill another prescription, the patient is deceased, or they changed residence.

### 3.2.1 Prescription Verification

Following initial patient enrollment on processing of a patient's first TIRF medicine prescription, pharmacies verified for all subsequent prescriptions that both the prescriber and patient were enrolled in the TIRF REMS Access program prior to dispensing. Prescription verification was not required for inpatient use of TIRF medicines.

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

On receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the pharmacist entered the prescription details in their PMS and sent the transaction to the TIRF REMS Access program via a switch provider. The TIRF REMS Access program used this transaction data to automatically transfer patient details into the TIRF REMS Access database for enrollment.

For all prescriptions, the REMS database was then interrogated, via the switch provider, to validate the REMS edits (i.e., met the TIRF REMS Access program requirements).

In the case of a valid prescription, a billing request was sent to the payer by the switch provider. Once the payer authorized payment the switch provider then authorized the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which was captured by the TIRF REMS Access program.

If the prescription was not valid (e.g. one of the stakeholders was not enrolled), the TIRF REMS Access program rejected the claim (prior to the claim being forwarded to the payer) and the pharmacy received a rejection notice from the switch provider. This automated feedback

indicated the reason for rejection, instructed the pharmacist not to dispense the TIRF medicine, and notified the pharmacist to contact the TIRF REMS Access program Call Center for further information.

### 3.3 Implementation System

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

#### 3.3.1 Wholesaler/Distribution Enrollment and Fulfillment

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

For the purpose of the TIRF REMS Access program, the term distributor refers to wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors received a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies. The distributor's authorized representative reviewed the distributor program materials. The distributor's authorized representative must complete and sign the Distributor Enrollment Form and faxed it to the TIRF REMS Access program. TIRF Sponsors did not ship TIRF medicines to any distributor who had not completed and signed the enrollment form.

#### 3.3.2 The TIRF REMS Access Program Compliance

TIRF Sponsors monitored prescriber, inpatient and outpatient pharmacy, and wholesaler/distributor activities for compliance with TIRF REMS Access program requirements. Corrective action (e.g., re-education, additional monitoring, process revision, stakeholder inactivation) was instituted by the TIRF Sponsors as appropriate if noncompliance was found.

Based on monitoring and evaluation of the elements to ensure safe use, TIRF Sponsors worked to improve implementation of these elements and to ensure compliance with the TIRF REMS Access program requirements, as applicable.

#### 3.3.3 TIRF REMS Access Program Call Center

The TIRF REMS Access program included a Call Center component. The Call Center was staffed by qualified and trained specialists, who provided TIRF REMS Access program support to patients, prescribers, pharmacies, and distributors.

## 4 REMS ASSESSMENT PLAN METHODS

The aim of the TIRF REMS Access program's evaluation was to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations were used in an effort to improve the processes, as needed.

## 4.1 Data Sources

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

### 4.1.1 TIRF REMS Access Program Outreach

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

1. Number of Dear HCP letters mailed to prescribers (by date)
2. Number of returned mailings of Dear HCP letters to prescribers.
3. Number of Pharmacist letters mailed to pharmacies (by date)
4. Number of returned mailings of Pharmacist letters to pharmacies

### 4.1.2 The TIRF REMS Access Program and Product Utilization Statistics

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

5. Number of new patients enrolled by state (Section 5.2.2)
6. Number of patients inactivated (Section 5.2.2)
7. Number of attempts needed for prescribers to successfully complete Knowledge Assessments (Section 5.2.3)
    - Method of completion
8. Number of new prescribers enrolled by state (Section 5.2.3)
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
9. Number of prescribers who are inactivated (Section 5.2.3)
10. Number of new pharmacies enrolled by type (inpatient or outpatient), by state (Section 5.2.4)
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
11. Number of pharmacies that are inactivated by type (inpatient or outpatient) (Section 5.2.4)

12. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments (Section 5.2.4)
13. Dispensing activity for enrolled outpatient pharmacies (Section 5.2.5)
    - Total number of prescriptions authorized
    - Total number of prescriptions rejected for safety (description of safety issues and any interventions or corrective actions taken)
14. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome) (Section 5.2.5)
15. Number of wholesalers/distributors inactivated, total (Section 5.2.6)
16. Number of new wholesalers/distributors enrolled (Section 5.2.6)
    - Method of enrollment
    - Number of incomplete forms
17. Number of days between enrollment and receipt of a PPAF (Section 5.2.7)
    - Method of PPAF submission
18. Number of prescriptions dispensed per patient during the first 10 days after patient enrollment with and without a PPAF in place. (Section 5.2.7)
    - A histogram of the number of days between passive enrollment and receipt of a PPAF. Stratify by the method of PPAF submission
    - A histogram of the number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment stratified by whether there is a PPAF in place.

### 4.1.3 Program Infrastructure and Performance

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

19. Assessment of process for pharmacies to upgrade their PMS (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems) (Section 5.3.1)
20. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem) (Section 5.3.2)
21. Call center report (Section 5.3.3)
    a. Summary of frequently asked questions
    b. Problems reported
22. Description of corrective actions taken to address program/system problems (Section 5.4)

23. Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area (Section 5.4.1)
24. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays (Section 5.4.2)

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

25. Reports identified of inadvertent enrollment deactivations (Section 5.5.1)
26. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code) (Section 5.5.2)
27. Reports of failure of re-enrollment notifications to reach stakeholders (Section 5.5.3)
28. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection (Section 5.5.4)

### 4.1.4 Safety Surveillance

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

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

- FDA adverse event reporting system (AERS) database using signal detection methods for TIRF medicines to identify outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion period. See Appendix 11.1 for list of Medical Dictionary for Drug Regulatory Activities (MedDRA) Preferred Terms used.
- AAPCC (Appendix 11.2) data for TIRF medicines and unknown fentanyl products with inhalation or ingestion as routes of exposure.

All source data are on file at UBC and available upon request.

## 4.2 TIRF REMS Access Program Non-Compliance Plan

The TIRF REMS Access program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the non-compliance plan is to ensure that TRIG monitors the functioning of TIRF REMS Access program and identifies and investigates deviations and non compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program.

A TIRF REMS Access program Non-Compliance Review Team (NCRT) will be created and a detailed plan for compliance monitoring will be created and implemented. The team will have membership from the companies of the TRIG. A detailed plan for the TIRF REMS Access

program will be created and implemented by the team. The NCRT will regularly review the following data sources for non-compliance or deviation from program procedures.

Those potential sources include:

- TIRF REMS Assessment reports
- REMS database activity
- TIRF REMS Access program Call Center
- Data Requests and Audits

Until the NCRT is instituted, all potential non-compliance events are reviewed individually by the TIRF REMS Access program to determine appropriate corrective action, if any.

#### 4.2.1 Corrective Action Measures

Stakeholders that fail to comply with one or more elements of the TIRF REMS Access program will be subject to corrective action. Corrective actions resulting from non-compliance will be determined by the TIRF REMS Access program according to the severity of the action.

## 5 RESULTS

### 5.1 TIRF REMS Access Program Outreach

#### 5.1.1 Dear Healthcare Professional Letters [Metric 1-4]

Prior to the launch of the TIRF REMS Access program, letters were sent to pharmacies and prescribers already enrolled in an individual TIRF REMS program. The first mailing for transition stakeholders occurred on 21 February 2012 and 22 February 2012 and the second mailing to a broader targeted stakeholder population occurred over a 10-day timeframe from 27 February 2012 through 09 March 2012. For the transition mailing there were a total of 5,855 Dear Healthcare Professional letters mailed: 4158 letters were mailed to prescribers, 1593 letters were mailed to outpatient pharmacies, 88 letters were mailed to inpatient pharmacies, and 16 were mailed to distributors (see Table 2). For the targeted mailing there were a total of 83,390 Dear Healthcare Professional letters mailed: 16,713 were mailed to prescribers, 60,737 were mailed to outpatient pharmacies, and 5,912 letters were mailed to inpatient pharmacies. Distributor letters were e-mailed to 28 distributors.

Over all the mailings, a total of 338 letters and e-mails were returned: 304 letters in March, 22 letters in April, and 10 letters in May (number of letters returned or reasons for the returns were not tracked by stakeholder). Two distributor letters that were sent via e-mail bounced back, one on 14 February 2012 and the second on 20 February 2012. In each case, alternate e-mail addresses were obtained and the e-mails were resent on the same day.

**Table 2: Number of Mailed Dear Healthcare Professional and Distributor Letters Current Reporting Period: 28 December 2011 to 27 April 2012**

| | Number of Letters Mailed N |
|---|---|
| Transition Stakeholder Dear HCP Mailing[a] | |
| Prescriber | 4158 |
| Outpatient Pharmacy | 1593 |
| Inpatient Pharmacy | 88 |
| Distributor | 16 |
| **Total** | **5,855** |
| | |
| Target Stakeholder Dear HCP Mailing[b] | |
| Prescriber | 16,713 |
| Outpatient Pharmacy | 60,737 |
| Inpatient Pharmacy | 5,912 |
| Distributor | 28 |
| **Total** | **83,390** |
| | |
| **Total Returned Mailings** | **338** |
| | |

[a] Transition Stakeholder Dear Healthcare Professional letters were mailed on 21 February 2012 and 22 February 2012. Transition Distributor letters were mailed between 14 February 2012 and 21 February 2012.
[b] Target Stakeholder Dear Healthcare Professional letters were mailed between 27 February 2012 and 09 March 2012. Target Stakeholder Distributor letters were e-mailed between 14 February 2012 and 21 February 2012.
Source: Data on file.

## 5.2 REMS Program Utilization

The total number and geographic distribution is described below of all enrolled stakeholders (prescribers, patients, distributors, outpatient independent and inpatient pharmacies, corporate chain pharmacy offices and chain pharmacy stores), stakeholder enrollment and inactivations, dispensing activities, and barriers or delays in patient access.

### 5.2.1 Independent TIRF REMS Program Transitioned Stakeholders

As of 12 March 2012, records for patients, prescribers, pharmacies, and distributors actively enrolled in independent TIRF REMS programs (i.e., enrollments were completed) were transitioned into the TIRF REMS Access program. The numbers of enrolled, transitioned stakeholders are shown below by stakeholder type (Table 3).

**Table 3: Transition Enrollment Statistics by Stakeholder Type: 28 December 2011 to 27 April 2012**

| Stakeholder Type | Transition Enrollment Statistics |
|---|---|
| Prescribers | 4,530 |
| Patients | 506 |
| Distributors | 22 |
| Outpatient Independent Pharmacies | 216 |
| Inpatient Pharmacies | 131 |
| Corporate Chain Pharmacy Offices | 52 |
| Chain Pharmacy Stores | 26,493 |

Source: Data on file.

Where applicable, these stakeholders are included in the metrics reported for the TIRF REMS Access program.

### 5.2.2 Patient Enrollment [Metric 5 and 6]

During the current reporting period, there were 7,783 patients from all 50 states, the District of Columbia and Puerto Rico who were enrolled in the REMS program, i.e., they had prescription activity during the current reporting period or transitions from individual TIRF REMS programs (Table 4). The following states had the highest proportion of enrolled patients: California (10.7%), Florida (5.8%), New Jersey (5.4%), Texas (5.4%), New York (4.6%), and Pennsylvania (3.1%). For 30.4% of patients, state/territory was unknown. Location is not reported for all patients who transitioned into the TIRF REMS Access program because it was not available for all patients from all independent TIRF REMS programs. Additionally, patients enrolled in the TIRF REMS Access program who sign the PPAF provide consent for data use in reporting; therefore, location cannot be reported on enrolled patients who do not have a PPAF on file. For patients who submitted more than one PPAF, the location is recorded from the first completed PPAF received.

There were no patients inactivated during the reporting period (not shown in Table 3; Data Sources: Table 6c: MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_050420121711.txt).

**Table 4: Patient Enrollment and Geographic Distribution**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Newly Enrolled Patients[c]** | 7,783 | 7,783 |
| | | |
| **State/Territory of Patient Primary Address[d]** | | |
| Unknown | 2,367 (30.4%) | 2,367 (30.4%) |
| Alabama | 78 (1.0%) | 78 (1.0%) |
| Alaska | 19 (0.2%) | 19 (0.2%) |
| Arizona | 109 (1.4%) | 109 (1.4%) |
| Arkansas | 21 (0.3%) | 21 (0.3%) |
| California | 830 (10.7%) | 830 (10.7%) |
| Colorado | 175 (2.3%) | 175 (2.3%) |
| Connecticut | 91 (1.2%) | 91 (1.2%) |
| Delaware | 40 (0.5%) | 40 (0.5%) |
| Florida | 448 (5.8%) | 448 (5.8%) |
| Georgia | 143 (1.8%) | 143 (1.8%) |
| Hawaii | 12 (0.2%) | 12 (0.2%) |
| Idaho | 17 (0.2%) | 17 (0.2%) |
| Illinois | 171 (2.2%) | 171 (2.2%) |
| Indiana | 97 (1.3%) | 97 (1.3%) |
| Iowa | 19 (0.2%) | 19 (0.2%) |
| Kansas | 56 (0.7%) | 56 (0.7%) |
| Kentucky | 47 (0.6%) | 47 (0.6%) |
| Louisiana | 26 (0.3%) | 26 (0.3%) |
| Maine | 10 (0.1%) | 10 (0.1%) |
| Maryland | 137 (1.8%) | 137 (1.8%) |
| Massachusetts | 51 (0.7%) | 51 (0.7%) |
| Michigan | 167 (2.2%) | 167 (2.2%) |
| Minnesota | 25 (0.3%) | 25 (0.3%) |
| Mississippi | 23 (0.3%) | 23 (0.3%) |
| Missouri | 66 (0.9%) | 66 (0.9%) |
| Montana | 8 (0.1%) | 8 (0.1%) |
| Nebraska | 19 (0.2%) | 19 (0.2%) |

(continued)

**Table 4: Patient Enrollment and Geographic Distribution**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| Nevada | 47 (0.6%) | 47 (0.6%) |
| New Hampshire | 12 (0.2%) | 12 (0.2%) |
| New Jersey | 420 (5.4%) | 420 (5.4%) |
| New Mexico | 12 (0.2%) | 12 (0.2%) |
| New York | 355 (4.6%) | 355 (4.6%) |
| North Carolina | 161 (2.1%) | 161 (2.1%) |
| North Dakota | 9 (0.1%) | 9 (0.1%) |
| Ohio | 141 (1.8%) | 141 (1.8%) |
| Oklahoma | 84 (1.1%) | 84 (1.1%) |
| Oregon | 52 (0.7%) | 52 (0.7%) |
| Pennsylvania | 239 (3.1%) | 239 (3.1%) |
| Rhode Island | 15 (0.2%) | 15 (0.2%) |
| South Carolina | 49 (0.6%) | 49 (0.6%) |
| South Dakota | 3 (0.0%) | 3 (0.0%) |
| Tennessee | 120 (1.5%) | 120 (1.5%) |
| Texas | 422 (5.4%) | 422 (5.4%) |
| Utah | 94 (1.2%) | 94 (1.2%) |
| Vermont | 1 (0.0%) | 1 (0.0%) |
| Virginia | 100 (1.3%) | 100 (1.3%) |
| Washington | 101 (1.3%) | 101 (1.3%) |
| West Virginia | 14 (0.2%) | 14 (0.2%) |
| Wisconsin | 41 (0.5%) | 41 (0.5%) |
| Wyoming | 15 (0.2%) | 15 (0.2%) |
| District of Columbia | 3 (<0.1%) | 3 (<0.1%) |
| Guam | 0 | 0 |
| Puerto Rico | 1 (<0.1%) | 1 (<0.1%) |
| Virgin Islands | 0 | 0 |
| | | |

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

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

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

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

Data Source: Table 1c: MCK_UBC_TIRF_FDA_Reporting_Patient_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt

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

During the current reporting period, there were 6,750 prescribers from all 50 states, the District of Columbia, and Puerto Rico who were enrolled in the TIRF REMS program (Table 5). The majority of these enrolled prescribers (64.1%) transitioned from other independent TIRF REMS programs (i.e., one-time file upload); prescribers who were first enrolled after 12 March 2012 enrolled using the Web-based enrollment system (33.7%) and manually by fax (2.2%).

The highest enrolling state was California (12.0%), followed by Florida (6.8%), Texas (6.5%), New York (6.0%), Pennsylvania (5.9%), and New Jersey (5.7%); all other states had enrollment of <4.5%.

There were 60 incomplete prescriber enrollment forms received for prescribers who enrolled via fax. Multiple forms may have been submitted for the same prescriber, and a form may be incomplete for more than one reason. The majority of incomplete forms were incomplete due to missing physician signature date (66.7%), missing signature (66.7%), and missing e-mail (33.3%), invalid DEA (26.7%), and provided DEA does not have correct schedule for drug (26.7%).

Prescribers who enroll via Web do not submit forms. They move through a series of enrollment modules and, at any given time in the process, one or more modules may be incomplete. A prescriber cannot enroll via Web unless all modules and requirements are completed. Of prescribers who initiated enrollment via the Web and had not completed enrollment as of the last date of the current reporting period (27 April 2012; data on file), the reasons for incomplete enrollment that represented at least 80.0% of those enrolling via Web were no attestation (469, 84.81%) and training not complete (469, 84.81%).

**Table 5: Prescriber Enrollment**

| | **Current Reporting Period[a] 28DEC2011 to 27APR2012** | **Cumulative[a,b] 28DEC2011 to 27APR2012** |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Newly Enrolled Prescribers[c]** | 6,747[d] | 6,747[d] |
| | | |
| **Method of Successful New Enrollments[e]** | | |
| Web | 2,274 (33.7%) | 2,274 (33.7%) |
| Fax | 147 (2.2%) | 147 (2.2%) |
| One-time file upload | 4,326 (64.1%) | 4,326 (64.1%) |
| | | |

(continued)

**Table 5: Prescriber Enrollment**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| **State/Territory of Prescriber Primary Address[f]** | | |
| Alabama | 102 (1.5%) | 102 (1.5%) |
| Alaska | 15 (0.2%) | 15 (0.2%) |
| Arizona | 203 (3.0%) | 203 (3.0%) |
| Arkansas | 47 (0.7%) | 47 (0.7%) |
| California | 811 (12.0%) | 811 (12.0%) |
| Colorado | 153 (2.3%) | 153 (2.3%) |
| Connecticut | 103 (1.5%) | 103 (1.5%) |
| Delaware | 23 (0.3%) | 23 (0.3%) |
| Florida | 458 (6.8%) | 458 (6.8%) |
| Georgia | 191 (2.8%) | 191 (2.8%) |
| Hawaii | 10 (0.2%) | 10 (0.2%) |
| Idaho | 13 (0.2%) | 13 (0.2%) |
| Illinois | 238 (3.5%) | 238 (3.5%) |
| Indiana | 199 (3.0%) | 199 (3.0%) |
| Iowa | 17 (0.3%) | 17 (0.3%) |
| Kansas | 49 (0.7%) | 49 (0.7%) |
| Kentucky | 61 (0.9%) | 61 (0.9%) |
| Louisiana | 76 (1.1%) | 76 (1.1%) |
| Maine | 17 (0.3%) | 17 (0.3%) |
| Maryland | 253 (3.7%) | 253 (3.7%) |
| Massachusetts | 95 (1.4%) | 95 (1.4%) |
| Michigan | 171 (2.5%) | 171 (2.5%) |
| Minnesota | 63 (0.9%) | 63 (0.9%) |
| Mississippi | 31 (0.5%) | 31 (0.5%) |
| Missouri | 99 (1.5%) | 99 (1.5%) |
| Montana | 15 (0.2%) | 15 (0.2%) |
| Nebraska | 29 (0.4%) | 29 (0.4%) |
| Nevada | 49 (0.7%) | 49 (0.7%) |
| New Hampshire | 33 (0.5%) | 33 (0.5%) |
| New Jersey | 385 (5.7%) | 385 (5.7%) |
| New Mexico | 16 (0.2%) | 16 (0.2%) |
| New York | 403 (6.0%) | 403 (6.0%) |

(continued)

**Table 5: Prescriber Enrollment**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| North Carolina | 294 (4.3%) | 294 (4.3%) |
| North Dakota | 7 (0.1%) | 7 (0.1%) |
| Ohio | 215 (3.2%) | 215 (3.2%) |
| Oklahoma | 68 (1.0%) | 68 (1.0%) |
| Oregon | 62 (0.9%) | 62 (0.9%) |
| Pennsylvania | 395 (5.9%) | 395 (5.9%) |
| Rhode Island | 13 (0.2%) | 13 (0.2%) |
| South Carolina | 60 (0.9%) | 60 (0.9%) |
| South Dakota | 4 (0.1%) | 4 (0.1%) |
| Tennessee | 226 (3.4%) | 226 (3.4%) |
| Texas | 438 (6.5%) | 438 (6.5%) |
| Utah | 98 (1.5%) | 98 (1.5%) |
| Vermont | 4 (0.1%) | 4 (0.1%) |
| Virginia | 165 (2.5%) | 165 (2.5%) |
| Washington | 129 (1.9%) | 129 (1.9%) |
| West Virginia | 28 (0.4%) | 28 (0.4%) |
| Wisconsin | 96 (1.4%) | 96 (1.4%) |
| Wyoming | 5 (0.1%) | 5 (0.1%) |
| | | |
| District of Columbia | 13 (0.2%) | 13 (0.2%) |
| Guam | 0 | 0 |
| Puerto Rico | 1 (<0.1%) | 1 (<0.1%) |
| Virgin Islands | 0 | 0 |
| | | |
| **Distribution of Reasons for Incomplete Prescriber Enrollment Forms Received for Fax-Enrolled Prescribers[g, h]** | 60[i] | 60[i] |
| Missing Physician Signature Date | 40 (66.7%) | 40 (66.7%) |
| Missing Signature | 40 (66.7%) | 40 (66.7%) |
| Missing Email | 20 (33.3%) | 20 (33.3%) |

(continued)

**Table 5: Prescriber Enrollment**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| Invalid DEA | 16 (26.7%) | 16 (26.7%) |
| Provided DEA does not have Correct Schedule for this Drug | 16 (26.7%) | 16 (26.7%) |
| Invalid NPI | 8 (13.3%) | 8 (13.3%) |
| Missing NPI Number | 6 (10.0%) | 6 (10.0%) |
| Missing State Medical License Number | 6 (10.0%) | 6 (10.0%) |
| Missing DEA Number | 2 (3.3%) | 2 (3.3%) |
| Missing Fax Number | 1 (1.7%) | 1 (1.7%) |
| | | |

Note: Percentages are based on the total number (N) of prescribers for the period except for counts of incomplete forms.
[a] The table reflects only enrolled prescribers who completed enrollment via fax.
[b] Cumulative is defined as sum of consecutive reporting periods.
[c] Prescribers enrolled in this time period and still enrolled at the end of the time period. *New Prescriber* is defined as having passed Knowledge Assessment and completed enrollment form and does not include prescriber re-enrollments.
[d] Includes prescribers who transitioned into the TIRF REMS Access program from other independent TIRF REMS programs.
[e] Percentage is based on the number of prescribers new to the TIRF REMS Access program, including prescribers that transitioned from other independent TIRF REMS programs.
[f] Enrolled prescribers are classified by their primary address as recorded on the Prescriber Enrollment Form.
[g] Percentage is based on the total number of incomplete forms received in the reporting period. Forms may be incomplete for more than one reason and more than one incomplete form received for a unique prescriber.
[h] Some stakeholders may have attempted enrollment via the Web.
[i] Does not include prescribers who transitioned into the TIRF REMS Access program from other independent TIRF REMS programs.
Data Sources: Table 1a: MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_050420121711.txt; MCK_UBC_TIRF_FDA_Prescriber_Location_050420121711.txt

Prescribers who take 6 attempts to complete the Knowledge Assessment are "suspended" in the TIRF REMS Access program until a representative from the Call Center can conduct outreach to provide additional educational assistance.

A total of 199 prescribers were inactivated during the current reporting period with 195 transitioned prescribers (98.0%) inactivated due to expiration of enrollment period, 2 (1.0%) prescribers were deceased, and 2 (1.0%) opted out of the program (Table 6).

**Table 6: Prescriber Inactivations**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Inactivated Prescribers** | 199 | 199 |
| | | |
| **Reason(s) For Inactivation[c]** | | |
| Enrollment Expired | 195 (98.0%) | 195 (98.0%) |
| Deceased | 2 (1.0%) | 2 (1.0%) |
| Program Opt-Out | 2 (1.0%) | 2 (1.0%) |
| | | |

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

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

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

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

Data Sources: Table 6a: MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_050420121711.txt

Among 2,423 newly enrolled prescribers who attempted and completed the knowledge assessments, 90.5% completed them via the Web and 9.5% completed them via fax (Table 7). Most prescribers passed the knowledge assessments on the first attempt (43.5%) or second attempt (32.9%). Seventy-eight (3.2%) prescribers enrolled during this assessment period required more than 4 attempts to successfully complete the knowledge assessments.

**Table 7: Enrolled Prescriber Completed Knowledge Assessments and Number of Attempts to Complete**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Enrolled Prescribers Successfully Completing Knowledge Assessment (KA)** | 2,423 | 2,423 |
| | | |
| **Method of KA Completion** | | |
| The Web | 2,193 (90.5%) | 2,193 (90.5%) |
| Fax | 230 (9.5%) | 230 (9.5%) |
| | | |

(continued)

**Table 7: Enrolled Prescriber Completed Knowledge Assessments and Number of Attempts to Complete**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| **Number of Prescribers with One or More Attempts to Successfully Complete Knowledge Assessment[b]** | | |
| One attempt | 1,054 (43.5%) | 1,054 (43.5%) |
| Two attempts | 797 (32.9%) | 797 (32.9%) |
| Three attempts | 380 (15.7%) | 380 (15.7%) |
| Four attempts | 114 (4.7%) | 114 (4.7%) |
| Five attempts | 46 (1.9%) | 46 (1.9%) |
| Six attempts | 24 (1.0%) | 24 (1.0%) |
| Greater than six attempts | 8 (0.3%) | 8 (0.3%) |
| | | |

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

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

[b] Limited to successfully enrolled prescribers completing a Knowledge Assessment.

Data Sources: Table 2a: MCK_UBC_TIRF_FDA_Reporting_KA_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt

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

Implementation of the TIRF REMS Access program for closed system pharmacies has been deferred to 30 June 2012. Therefore, this assessment report does not include any data from the closed system pharmacies.

During the current reporting period, there were 35,407 outpatient pharmacies from all 50 states, as well as the District of Columbia, Guam, Puerto Rico, and the Virgin Islands that were enrolled in the REMS program including corporate pharmacy stores (89.1%), independent outpatient pharmacies (9.6%), inpatient pharmacies (1.1%), and corporate pharmacy headquarters (0.2%) (Table 8).

The states where pharmacies had the highest proportion of enrolled pharmacies included California (9.7%), Florida (8.1%), Texas (6.5%), New York (5.9%), Pennsylvania (5.2%), Ohio (4.3%), Illinois (4.0%), Georgia (3.8%), Michigan (3.8%), New Jersey (3.4%), North Carolina (3.2%); all other states had enrollment ≤2.8%.

As shown in Table 8, the method of enrollment for the majority of pharmacies was via their corporate chain (89.7%; i.e., enrollment occurred via file enrollment upload), followed by those that enrolled via the Web (10.1%), or manually by fax (0.2%).

There were 75 incomplete pharmacy enrollment forms received for pharmacies that enrolled via fax and the reasons most often reported for incompleteness were missing DEA number (16.0%), invalid DEA number (13.3%), missing NPI number (9.3%), and invalid NPI (6.7%). It should be noted that each form may have multiple reasons and could have been submitted multiple times.

As described for prescribers, pharmacies that enroll via Web do not submit forms, but instead move through a series of modules. At any given time in the process, one or more modules may be incomplete. Pharmacies cannot enroll via Web unless all modules/requirements are completed. There were a number of outpatient (N=1303) and inpatient pharmacies (N=61) who initiated enrollment via the Web but did not complete enrollment as of the last date of the current reporting period (27 April 2012; data on file). The major reasons for incomplete enrollment of outpatient pharmacies (representing at least 80.0% of all incomplete reasons) were as follows: not agreed to terms and conditions (625, 47.97%), pending test transaction verification (369, 28.32%), and no attestation (311, 23.87%). The single reason for incomplete enrollment of inpatient pharmacies that represented at least 80.0% of incomplete reasons was no attestation (53, 86.89%).

There were no inpatient or outpatient pharmacies deactivated during this reporting period (not shown in Table 8; Data Sources: Table 6b: MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_050420121711.txt).

**Table 8: Pharmacy Enrollment**

| | **Current Reporting Period 28DEC2011 to 27APR2012** | **Cumulative[a] 28DEC2011 to 27APR2012** |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Enrolled Pharmacies[b]** | 35,407 [c] | 35,407 [c] |
| Independent Outpatient | 3,386 (9.6%) | 3,386 (9.6%) |
| Corporate Pharmacy Headquarters | 79 (0.2%) | 79 (0.2%) |
| Corporate Pharmacy Stores | 31,545 (89.1%) | 31,545 (89.1%) |
| Inpatient | 397 (1.1%) | 397 (1.1%) |
| | | |
| **Method of Successful Enrollments[d]** | | |
| The Web | 3,574 (10.1%) | 3,574 (10.1%) |
| Fax | 79 (0.2%) | 79 (0.2%) |
| File (file enrollment upload) | 31,754 (89.7%) | 31,754 (89.7%) |
| | | |

(continued)

**Table 8: Pharmacy Enrollment**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| **State/Territory of Pharmacy Primary Address[e]** | | |
| Alabama | 596 (1.7%) | 596 (1.7%) |
| Alaska | 52 (0.2%) | 52 (0.2%) |
| Arizona | 789 (2.2%) | 789 (2.2%) |
| Arkansas | 216 (0.6%) | 216 (0.6%) |
| California | 3,416 (9.7%) | 3,416 (9.7%) |
| Colorado | 551 (1.6%) | 551 (1.6%) |
| Connecticut | 457 (1.3%) | 457 (1.3%) |
| Delaware | 147 (0.4%) | 147 (0.4%) |
| Florida | 2,852 (8.1%) | 2,852 (8.1%) |
| Georgia | 1,326 (3.8%) | 1,326 (3.8%) |
| Hawaii | 95 (0.3%) | 95 (0.3%) |
| Idaho | 152 (0.4%) | 152 (0.4%) |
| Illinois | 1,423 (4.0%) | 1,423 (4.0%) |
| Indiana | 835 (2.4%) | 835 (2.4%) |
| Iowa | 209 (0.6%) | 209 (0.6%) |
| Kansas | 259 (0.7%) | 259 (0.7%) |
| Kentucky | 471 (1.3%) | 471 (1.3%) |
| Louisiana | 463 (1.3%) | 463 (1.3%) |
| Maine | 154 (0.4%) | 154 (0.4%) |
| Maryland | 739 (2.1%) | 739 (2.1%) |
| Massachusetts | 858 (2.4%) | 858 (2.4%) |
| Michigan | 1,347 (3.8%) | 1,347 (3.8%) |
| Minnesota | 525 (1.5%) | 525 (1.5%) |
| Mississippi | 252 (0.7%) | 252 (0.7%) |
| Missouri | 544 (1.5%) | 544 (1.5%) |
| Montana | 93 (0.3%) | 93 (0.3%) |
| Nebraska | 176 (0.5%) | 176 (0.5%) |
| Nevada | 305 (0.9%) | 305 (0.9%) |
| New Hampshire | 172 (0.5%) | 172 (0.5%) |
| New Jersey | 1,190 (3.4%) | 1,190 (3.4%) |
| New Mexico | 161 (0.5%) | 161 (0.5%) |
| New York | 2,098 (5.9%) | 2,098 (5.9%) |
| North Carolina | 1,139 (3.2%) | 1,139 (3.2%) |

(continued)

**Table 8: Pharmacy Enrollment**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| North Dakota | 44 (0.1%) | 44 (0.1%) |
| Ohio | 1,529 (4.3%) | 1,529 (4.3%) |
| Oklahoma | 336 (1.0%) | 336 (1.0%) |
| Oregon | 385 (1.1%) | 385 (1.1%) |
| Pennsylvania | 1,830 (5.2%) | 1,830 (5.2%) |
| Rhode Island | 157 (0.4%) | 157 (0.4%) |
| South Carolina | 630 (1.8%) | 630 (1.8%) |
| South Dakota | 46 (0.1%) | 46 (0.1%) |
| Tennessee | 833 (2.4%) | 833 (2.4%) |
| Texas | 2,317 (6.5%) | 2,317 (6.5%) |
| Utah | 275 (0.8%) | 275 (0.8%) |
| Vermont | 78 (0.2%) | 78 (0.2%) |
| Virginia | 984 (2.8%) | 984 (2.8%) |
| Washington | 750 (2.1%) | 750 (2.1%) |
| West Virginia | 284 (0.8%) | 284 (0.8%) |
| Wisconsin | 575 (1.6%) | 575 (1.6%) |
| Wyoming | 63 (0.2%) | 63 (0.2%) |
| District of Columbia | 84 (0.2%) | 84 (0.2%) |
| Guam | 1 (<0.1%) | 1 (<0.1%) |
| Puerto Rico | 142 (0.4%) | 142 (0.4%) |
| Virgin Islands | 2 (<0.1%) | 2 (<0.1%) |
| | | |
| **Number of Incomplete Pharmacy Enrollment Forms Received for Fax Enrolled Pharmacies[f]** | 75[g] | 75[g] |
| Missing DEA Number | 12 (16.0%) | 12 (16.0%) |
| Invalid DEA | 10 (13.3%) | 10 (13.3%) |
| Missing NPI Number | 7 (9.3%) | 7 (9.3%) |
| Invalid NPI | 5 (6.7%) | 5 (6.7%) |
| Invalid NCPDP | 4 (5.3%) | 4 (5.3%) |
| Missing NCPDP Number | 4 (5.3%) | 4 (5.3%) |
| Missing Email | 3 (4.0%) | 3 (4.0%) |

(continued)

**Table 8: Pharmacy Enrollment**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| Missing State License Number | 2 (2.7%) | 2 (2.7%) |
| Missing Fax Number | 1 (1.3%) | 1 (1.3%) |
| | | |

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

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

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

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

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

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

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

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

Data Sources: Table 1b: MCK_UBC_TIRF_FDA_Reporting_Pharmacy_050420121711.txt;
MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt;
MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_050420121711.txt

A total of 2,183 enrolled authorized pharmacies completed the knowledge assessments (Table 9). The majority of pharmacies completed the knowledge assessments on the first attempt (37.6%) or the second attempt (38.8%). There were 7.5% of pharmacies that required four or more attempts to successfully complete the knowledge assessment.

**Table 9: Enrolled Authorized Pharmacist/Pharmacy Knowledge Assessments and Attempts Needed to Complete**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Authorized Pharmacists/Pharmacy Representatives Successfully Completing Knowledge Assessment** | 2,183 | 2,183 |
| | | |
| **Number of Authorized Pharmacists with One or More Attempts to Successfully Complete Knowledge Assessment[c]** | | |
| One attempt | 821 (37.6%) | 821 (37.6%) |
| Two attempts | 846 (38.8%) | 846 (38.8%) |
| Three attempts | 353 (16.2%) | 353 (16.2%) |

(continued)

**Table 9: Enrolled Authorized Pharmacist/Pharmacy Knowledge Assessments and Attempts Needed to Complete**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| Four attempts | 112 (5.1%) | 112 (5.1%) |
| Five attempts | 37 (1.7%) | 37 (1.7%) |
| Six attempts | 10 (0.5%) | 10 (0.5%) |
| Greater than six attempts | 4 (0.2%) | 4 (0.2%) |
| | | |

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

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

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

[c] Limited to successfully enrolled pharmacists.

Data Sources: Table 2b: MCK_UBC_TIRF_FDA_Reporting_KA_050420121711.txt ; MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt

### 5.2.5 Dispensing Activity [Metric 13 and 14]

At total of 14,175 prescriptions were authorized in the current reporting period. To be authorized, the prescriber must be enrolled, the pharmacy must be enrolled, and the outpatient can receive up to 3 fills without a PPAF in 10 days. Of those authorized prescriptions, 94.3% were dispensed (meaning authorized for dispensing by insurance or paid for in cash) (Table 10). Patients with prescriptions from multiple prescribers within an overlapping time frame were assessed, and no patient had more than 3 prescribers in a 6 month period (not shown in Table 9; Source Table 3b, Data Source: RHP_UBC_TIRF_FDA_Network_Data_04282012.txt).

**Table 10: Authorized Prescriptions Dispensed from Outpatient Pharmacies**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Authorized Prescriptions[b]** | 14,175 | 14,175 |
| | | |
| **Number of Authorized Prescriptions Dispensed[c]** | 13,371 (94.3%) | 13,371 (94.3%) |
| | | |

Note: Percentages are based on the total number (N) of authorized prescriptions for the period.

[a] Includes authorizations from pharmacies that transitioned into the TIRF REMS Access program from other independent TIRF REMS programs.

[b] Prescription successfully adjudicated for safety (i.e., successful REMS edit).

[c] Indicates number of prescriptions that were adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or paid for in cash.

Data Source: Table 3a, RHP_UBC_TIRF_FDA_Network_Data_04282012.txt

A total of 11,808 prescription claims were rejected for safety reasons (meaning the transaction failed to meet REMS requirements for prescriber and/or patient and/or pharmacy). A single prescription may have been submitted and rejected multiple times. The majority of safety reasons were due to prescriber ID not in TIRF REMS Access database (46.8%), PPAF incomplete (23.6%), patient zip code missing from claim (14.5%), or prescriber last name did not match name registered (10.0%).

Upon receiving an inbound call from a pharmacy provider, the TIRF REMS Access program Call Center Service Representative (CSR) worked to resolve the rejected transaction and to provide instructions on the corrective action needed to successfully process the transaction. CSR resolution process included asking a series of questions to determine the reason for the rejected claim and looking up the rejected transaction to view the actual data submitted on the transaction. Quick Reference Guides were used to provide specific instruction for correcting a rejected message. Corrective action included outreach and education to remedy rejected transaction processing.

**Table 11: Total Number of Prescriptions Rejected for Safety**

| | **Current Reporting Period[a] 28DEC2011 to 27APR2012** | **Cumulative[a] 28DEC2011 to 27APR2012** |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Prescription Claims Rejected for Safety** | 11,808 | 11,808 |
| | | |
| **Reasons For Rejection[b]** | | |
| Pharmacy not enrolled | 2,119 (17.9%) | 2,119 (17.9%) |
| Pharmacy enrollment incomplete or expired | 344 (2.9%) | 344 (2.9%) |
| System unavailable due to maintenance | 5 (<0.1%) | 5 (<0.1%) |
| Prescriber ID not submitted on claim | 104 (0.9%) | 104 (0.9%) |
| Prescriber ID not in TIRF REMS Access database | 5,529 (46.8%) | 5,529 (46.8%) |
| Prescriber last name did not match name registered | 1,175 (10.0%) | 1,175 (10.0%) |
| Prescriber enrollment incomplete or expired | 213 (1.8%) | 213 (1.8%) |
| Prescriber enrollment incomplete or expired and prescriber last name mismatch | 22 (0.2%) | 22 (0.2%) |
| DOB missing from claim | 9 (0.1%) | 9 (0.1%) |
| Patient first name missing from claim | 71 (0.6%) | 71 (0.6%) |
| Patient last name missing from claim | 26 (0.2%) | 26 (0.2%) |
| Patient zip code missing from claim | 1,712 (14.5%) | 1,712 (14.5%) |
| Multiple patients found | 1 (<0.1%) | 1 (<0.1%) |

(continued)

**Table 11: Total Number of Prescriptions Rejected for Safety**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| Prescriber decision to deactivate patient | 0 | 0 |
| Patient inactive ≥ 6 months and must resubmit PPAF | 0 | 0 |
| Patient deceased | 0 | 0 |
| Database failure | 0 | 0 |
| PPAF Incomplete | 2,790 (23.6%) | 2,790 (23.6%) |
| PPAF Terminated | 14 (0.1%) | 14 (0.1%) |
| | | |

Note: Percentages are based on the total number (N) of rejected prescriptions for the relevant period. *Rejected for Safety* is defined in this table to mean the prescription did not pass REMS edits

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

[b] A prescription may be rejected for more than one reason.

Data Source: Table 3c**:** RHP_UBC_TIRF_FDA_Network_Data_04282012.txt

### 5.2.6 Wholesaler/Distributor Enrollment [Metric 15 and 16]

During the current reporting period, 42 wholesalers/distributors were enrolled in the REMS program, and all were enrolled by fax (100.0%) (Table 12).

There were no incomplete forms received from wholesalers/distributors (Table 12), and no wholesaler/distributor enrollments had been inactivated (data not shown in Table 11; Data Sources Table 6d: MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_Status_History_050420121711.txt).

**Table 12: Wholesaler/Distributor Enrollment**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Wholesalers/Distributors Enrolled** | 42 | 42 |
| | | |
| **Method of Enrollment** | | |
| Fax | 42 (100.0%) | 42 (100.0%) |
| | | |

(continued)

**Table 12: Wholesaler/Distributor Enrollment**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a,b] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| **Number of Incomplete Wholesaler/ Distributor Enrollment Forms Received** | 0 | 0 |
| | | |

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

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

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

Data Source: Table 1d: MCK_UBC_TIRF_FDA_Reporting_Distributor_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt

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

A total of 5,799 PPAFs were submitted to the REMS program either via the Web (72.4%), by fax (16.6%), or forms were transitioned into the REMS program via other independent TIRF REMS programs (i.e., one time file upload; 11.0%). Most PPAFs (45.0%) were received on the same day as patient enrollment (31.1%) or between 1 and 10 days (13.9%); however 28.3% of forms were received between 21 and 30 days and 13.4% of forms were received greater than 30 days after enrollment (Table 13 and Figure 1).

There are 637 PPAFs received via file upload for transitioned patients, and 506 enrolled patients transitioned from independent TIRF REMS programs (see Section 5.2.1). Only one completed PPAF was transitioned per a unique patient from the independent TIRF REMS programs. Not all transitioned PPAFs are necessarily associated with an enrolled patient. PPAFs may be on file for patients who have not enrolled (i.e., not filled at least one prescription).

PPAFs for 200 enrolled patients had not been received as of the cutoff date for this report. No receipt of PPAF for an enrolled patient may indicate that the patient received one filled prescription without a PPAF and then never attempted to receive another prescription, the patient is deceased, changed residence, or opted out of the program.

**Table 13: Submission of Patient-Prescriber Agreements to the REMS Program**

| | Current Reporting Period[a] 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Patient-Prescriber Agreement Forms Submitted to REMS Program** | 5,799 | 5,799 |
| | | |
| **Method of PPAF Submission** | | |
| The Web | 4,200 (72.4%) | 4,200 (72.4%) |
| Fax | 962 (16.6%) | 962 (16.6%) |
| One-time file upload | 637 (11.0%) | 637 (11.0%) |
| | | |
| **Number of Forms Received by Days Elapsed between Patient Enrollment and Receipt of Patient-Prescriber Agreement by REMS Program** | | |
| Form Received Same Day | 1,802 (31.1%) | 1,802 (31.1%) |
| Form Received between 1 and 10 days | 804 (13.9%) | 804 (13.9%) |
| Form Received between 11 and 15 days | 275 (4.7%) | 275 (4.7%) |
| Form Received between 16 and 20 days | 303 (5.2%) | 303 (5.2%) |
| Form Received between 21 and 30 days | 1,641 (28.3%) | 1,641 (28.3%) |
| Form Received >30 days after Patient Enrollment | 774 (13.4%) | 774 (13.4%) |
| PPAF not yet received | 200 (3.5%) | 200 (3.5%) |
| | | |

Note: Percentages are based on the total number (N) of forms for the period.
[a] Includes patients that transitioned into the TIRF REMS Access program from other independent TIRF REMS programs.
Data Sources: Table 4a: MCK_UBC_TIRF_FDA_Reporting_PPAF_050420121711.txt;
MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt

**Figure 1: PPAF Receipt by Time Since Patient Enrollment.**

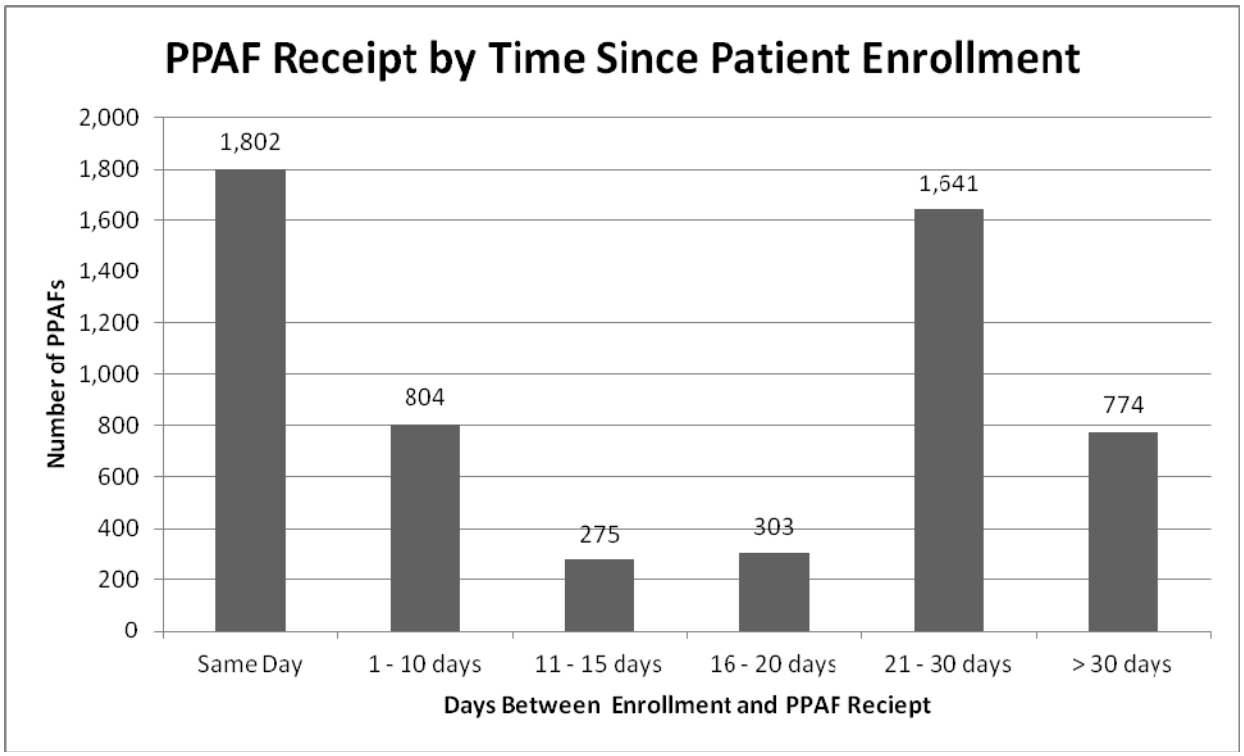


Figure Source: Table 4a: MCK_UBC_TIRF_FDA_Reporting_PPAF_050420121711.txt; MCK_UBC_TIRF_FDA_Reporting_Enrollment_050420121711.txt

A total of 8,668 prescriptions were dispensed to a total of 7,148 patients during the first 10 days after patient enrollment (Table 14 and Figure 2 below). There were a greater number of patients who had one prescription filled in the first 10 days without a PPAF compared with those patients with a PPAF (83.0% vs. 9.0%); however, a patient is eligible to receive up to 3 fills in the first 10 days after enrollment without a PPAF. For patients without a PPAF, the majority of patients (83.0%) received only 1 fill compared with 10.5% of patients who received more than 1 fill.

There were 29 patients who received more than 3 fills without a PPAF on file in a 10-day period. Root cause analysis on these transaction data is underway to determine which data elements permitted the transaction to pass through the REMS edits. The results of this investigation are ongoing and will be reported in the next reporting cycle.

**Table 14: Prescriptions Dispensed During the First 10 Days after Patient Enrollment**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative[a] 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of prescriptions dispensed to patients during the first 10 days after patient enrollment** | 8,668 | 8,668 |
| | | |
| **Number of patients dispensed a prescription during the first 10 days after patient enrollment** | 7,148 | 7,148 |
| | | |
| **With PPAF[b]** | | |
| 1 Fill | 644 (9.0%) | 644 (9.0%) |
| 2 Fills | 126 (1.8%) | 126 (1.8%) |
| 3 Fills | 22 (0.3%) | 22 (0.3%) |
| >3 Fills | 10 (0.1%) | 10 (0.1%) |
| | | |
| **Without a PPAF[b, c]** | | |
| 1 Fill | 5,931 (83.0%) | 5,931 (83.0%) |
| 2 Fills | 610 (8.5%) | 610 (8.5%) |
| 3 Fills | 115 (1.6%) | 115 (1.6%) |
| >3 Fills | 29 (0.4%) | 29 (0.4%) |
| | | |

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

[b] Percentages are based on the total number of patients (N=7,148) for the period. Sum of percentages *may* be greater than 100 due to patients receiving prescriptions with and without a PPAF during the grace period.

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

Data Source: Table 4b: RHP_UBC_TIRF_FDA_Network_Data_04282012.txt

**Figure 2: Number of Patients Dispensed a Prescription During the First 10 Days After Patient Enrollment.**

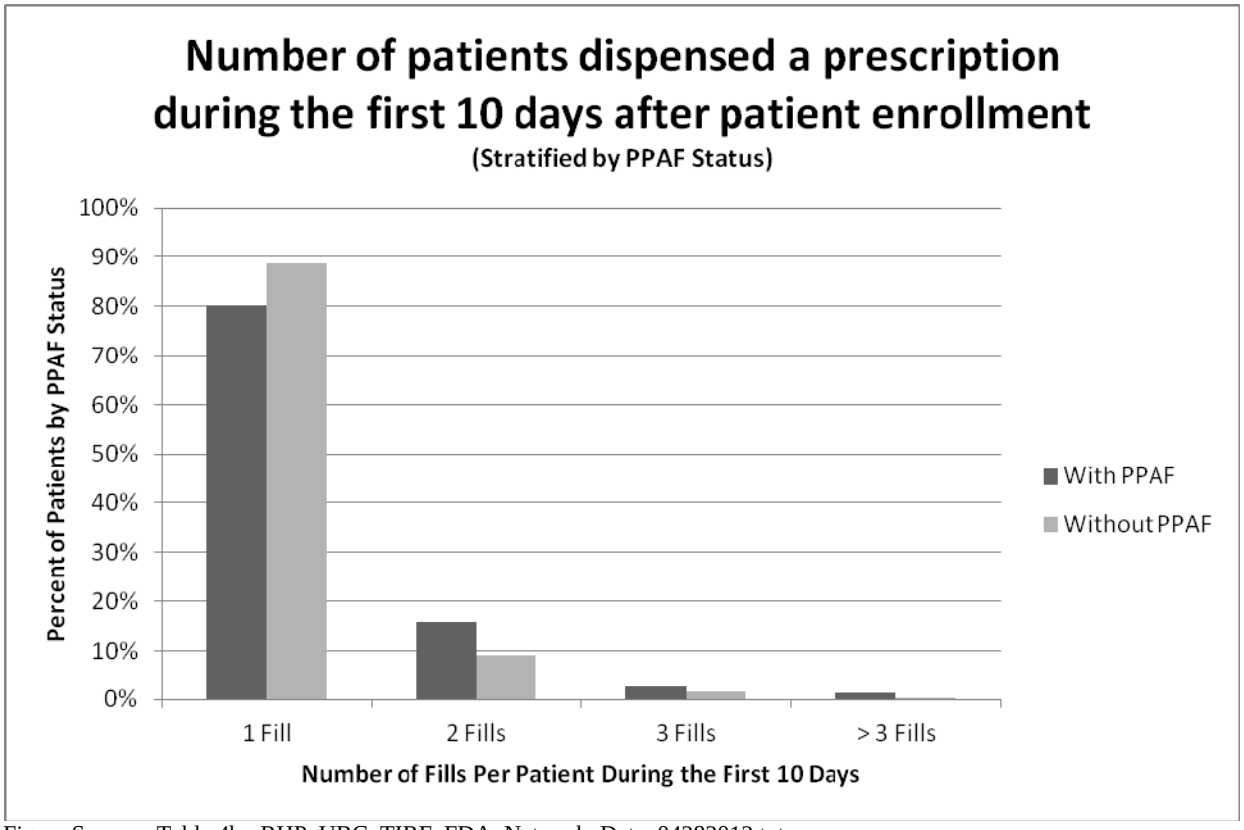


Figure Source: Table 4b: RHP_UBC_TIRF_FDA_Network_Data_04282012.txt

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

### 5.3.1 Pharmacy Management Systems [Metric 19]

Table 15 summarizes the time it took enrolled outpatient pharmacies to configure their PMS to communicate with the REMS program. Of 2,188 outpatient pharmacies that attempted to configure a PMS, 96.3% successfully reconfigured their systems and 3.7% did not complete configuration of their PMS within the reporting period. It took a mean of 0.9 days to configure, with a minimum of 0.0001 days and a maximum of approximately 42 days.

**Table 15: Configuration of Pharmacy Management System (PMS)**

| | Current Reporting Period 28DEC2011 to 27APR2012 | Cumulative 28DEC2011 to 27APR2012 |
|---|---|---|
| **Parameter** | **N (%)** | **N (%)** |
| | | |
| **Number of Outpatient Pharmacies Attempting to Configure PMS** | 2,188 | 2,188 |
| | | |
| **Number of Pharmacies with Incomplete Configuration of PMS[a]** | 81 (3.7%) | 81 (3.7%) |
| | | |
| **Number of Outpatient Pharmacies Successfully Completing Configuration of PMS[b]** | 2,107 (96.3%) | 2,107 (96.3%) |
| | | |
| **Time Required to Complete Configuration[c]** | | |
| Mean | 0.9205 | 0.9205 |
| Minimum | 0.0001 | 0.0001 |
| Maximum | 42.187 | 42.187 |
| | | |

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

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

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

Data Source: Table 5: RHP_UBC_TIRF_FDA_Network_Data_04282012.txt

### 5.3.2 Backup System for Prescription Validation [Metric 20]

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

### 5.3.3 REMS Call Center [Metric 21a, b]

Table 16 below shows reasons for contacting the REMS Call Center by frequency (%). For presentation in the report, the table cut-off is at least 80% of the total cumulative frequency of contact reasons. The most frequent reasons classified under the call reason were enrollment status inquiry (18.7%), claim rejection due to pharmacy REMS edit (12.4%), claim rejection due to prescriber REMS edit (10.7%), PPAF inquiry (8.8%), and PPAF follow up (7.9%). The call reasons listed below in Table 16 represent 83.80% of calls to the Call Center for the current reporting period.

**Table 16: Reasons and Frequency for Contacting the Call Center**

| Contact Reason | Current Reporting Period 28DEC2011 to 27APR2012 | | Cumulative 28DEC2011 to 27APR2012 | |
|---|---|---|---|---|
| | Frequency | Percent[a] | Cumulative Frequency | Cumulative Percent |
| Enrollment Status Inquiry | 4729 | 18.66 | 4729 | 18.66 |
| Claim Rejection Due to Pharmacy REMS Edit | 3145 | 12.41 | 3145 | 12.41 |
| Claim Rejection Due to Prescriber REMS Edit | 2722 | 10.74 | 2722 | 10.74 |
| PPAF Inquiry | 2228 | 8.79 | 2228 | 8.79 |
| PPAF Follow Up | 2010 | 7.93 | 2010 | 7.93 |
| General Program Questions | 1684 | 6.65 | 1684 | 6.65 |
| Claim Rejection Due to Patient REMS Edit | 1628 | 6.43 | 1628 | 6.43 |
| Enrollment Follow Up | 1575 | 6.22 | 1575 | 6.22 |
| Other/Misc[b] | 1511 | 5.96 | 1511 | 5.96 |

[a] The total percentage presented in the table is 83.80% of all reasons for contacting the Call Center.

[b] Other/misc include: request to change or update current information; transfers for pharmacy technical support; wrong number/hang-up/no one on the line; and, general REMS questions – non-TIRF specific.

Source: Data on file (The FREQ Procedure).

Problems or complaints that were reported to the REMS Call Center for review by the TIRF REMS Access program are summarized below:

**ID#1**
Issue: Several patients complained regarding inability to find enrolled prescriber in program because their prescriber is refusing to enroll and will no longer prescribe TIRF medicines.

Resolution: The TIRF REMS Access program Call Center reviewed options with callers. A call guideline will be created and an offer made to contact patient's prescriber. The original prescriber will be advised of other prescribers enrolled in the TIRF REMS Access program to potentially provide to and refer the patient.

**ID #2**
Issue: Patient frustrated with delay in receiving medication due to no PPAF on file. Three outbound PPAF reminder calls placed to prescriber from 17 March 2012 – 13 April 2012. Patient requested to file a complaint about the requirements of a PPAF. The patient stated she feels the requirement of a PPAF is a “threat” because program mandates that she does have to sign a PPAF, but also states that she will not receive medication until she does so.

Resolution: Case was reviewed and complaints will continue to be monitored. No further escalations were received from patient.

**ID #3**
Issue: Identified two examples of small institutions with multiple outpatient pharmacies where pharmacies share identifiers. The TIRF REMS Access program requires unique identifiers to enroll and process claims.

Resolution: At one institution, three outpatient pharmacies are located at different addresses. The pharmacies share the same pharmacy system, and no attempt had been made to request separate identifiers. Subsequently, all three of the pharmacy locations were successfully enrolled as outpatient pharmacies and are dispensing TIRF medicines. At the other institution, no outpatient pharmacy has been enrolled.

**ID #4**
Issue: Several Prescribers complained that the TIRF REMS program was contacting the office too often to follow-up on the status of missing PPAFs. An office can receive multiple calls for multiple patients each week.

Resolution:
TRIG evaluated the option to reduce number of outbound calls, however, felt it was important during the post launch period to follow-up often and reinforce the PPAF requirement with prescriber offices. No changes will be made at this time to reduce the number of outbound calls for missing PPAFs.

**ID #5**
Issue: Several pharmacist complaints were received regarding the process to change an authorized pharmacist or what is known as the 'designee'. When a change to the authorized pharmacist is needed, the new pharmacist is asked to complete and fax a completed enrollment form and Knowledge Assessment as an outpatient pharmacy. New authorized pharmacists were requesting that a change of name be completed without the need to send in new forms

Resolution:
Current process will remain unchanged. New pharmacist in charge must attest to the REMS requirements. Modifications to the 'change in designee' process may be considered in the future.

Additional Call Center issues that met the definition of non-compliance are presented in Section 6, Report #1, #2, and Report #10.

## 5.4 System Errors and Corrective Actions [Metric 22]

A brief summary of issues identified as system errors and their corrective actions is presented below. Additional system errors that met the definition of non-compliance are presented in Section 6, Reports # 5, 6, 7, 8, and 9.

System Error #1
Description: Customers were reporting issues logging into TIRF REMS Access program Web site related to their inability to use the 'forgot password' function. This was due to not transitioning some of the stakeholders' existing passwords over to TIRF REMS Access program from the independent TIRF REMS programs.

Root Cause: Record conversion issue from independent TIRF REMS programs into TIRF REMS Access program (insufficient test case).

Correction: The TIRF REMS Access program moved training records for affected records into TIRF REMS Access program database, and developed fax template to respond to the inquiries with instructions to transition stakeholders on how to register and create a new user name and password in the TIRF REMS Access program Web site.

System Error #2
Description: TIRF REMS Access program Web site URL not found when using search function on Bing.

Root Cause: Bing search engine link to TIRF REMS Access program was pointing to the coming soon link: http://www.tirfremsaccess.com/TirfUISplashWeb/index.html. Once program went live on 12 March 2012, this page was no longer available.

Correction: Removed http://www.tirfremsaccess.com/TirfUISplashWeb/index.html page from Web site to force a refresh for this search engine.

System Error #3
Description: Scope of Work (SOW) message is displaying for stakeholders who are already enrolled and accepted the SOW conditions. Users need to click OK to move past the message.

Root Cause: Defect in application that checked status of SOW completion, not found during QA; insufficient test case.

Correction: Interim solution communicated to Call Center representatives on 12 March 2012 that by clicking the OK button on the SOW screen, stakeholders can move into the dashboard and access appropriate functionality. The program was permanently fixed on 12 March 2012 so that for stakeholders who are already enrolled and have accepted the SOW conditions the SOW message is not displayed.

System Error #4
Description: The TIRF REMS Access program forecasted 550 activities per day based on independent TIRF REMS program volumes and projected additional activities. Upon implementation, the TIRF REMS Access program volume accelerated to 1500 inbound calls and 250 faxes per day and the reasons appeared to be related to the following: trouble-shooting rejected claims; high volume of new enrollments and program inquiry calls; Web enrollment inquiries; assisting pharmacy callers with updating their terms and conditions.

Root Cause: Underestimated Call Center activities

Correction: The following corrective actions were implemented: increased and trained 19 additional agents to handle Call Center activities; implemented voice mail during business hours (updated call flow); created fax templates to respond to callers frequently asked questions; postponed outbound call activity for incomplete enrollments; and instituted daily operation checkpoint meetings to monitor activities.

System Error #5:
PPAFs specific to the individual TIRF REMS programs were received by TIRF REMS Access program after go-live date of 12 March 2012 for new patients. In response, the TIRF REMS Access program allowed prescribers to submit PPAFs for newly enrolled patients using forms from individual TIRF REMS programs for 60-days from 12 March 2012 in order to allow patient access. During this time educational outreach was conducted to prescribers instructing on the use of the new PPAF form for the TIRF REMS Access program.

System Error #6:
Effective 12 March 2012, all prescription claims transmitted to the TIRF REMS Access program with an national drug code (NDC) code for a TIRF medicine are subject to REMS edits. However, the TIRF REMS Access program logic did not include an exclusion for processing claims with a Date of Service that predated 12 March 2012. After the go-live date of 12 March 2012, the TIRF REMS Access program continued to receive transactions with a Date of Service (DOS) dated prior to 12 March 2012 and these claims were rejected due to pharmacy REMS edits. During the assessment period of 12 March 2012 thru 27 April 2012, there were 42 transactions that were impacted by this issue with DOS prior to March 12 and rejected.

The TIRF REMS Access program developed a manual process that would allow transactions with a DOS prior to the 12 March 2012 to bypass all REMS edits on a case-by-case basis, and the list was placed into production on 15 March 2012. The exclusion list is tailored to only allow transactions with a DOS prior to 12 March 2012 to bypass the REMS network. Prior to bypassing the REMS network, TIRF REMS Access program conducts outreach to the pharmacy to confirm that the prescription was dispensed prior to 12 March 2012. Once confirmation has been received, the Service Provider ID, prescription number, and DOS are manually added to the exclusion list. The transaction is then re-processed by the pharmacy and sent to the Third Party Administrator for payment. This error delayed payment processing but did not have any

impact on patient access to TIRF medicines, and only applied to NDC codes that were not part of an individual TIRF REMS program.

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

During the current reporting period, no reports of lack of enrolled pharmacies were received.

### 5.4.2 Delays after Prescription Denial [Metric 24]

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

For the current assessment period:

- The mean prescription conversion time was 0 days, 7.759 hours.
- The median prescription conversion time was 0 days, 1.101 hours.
- The minimum prescription conversion was 0 days, 0.001 hours.
- The maximum prescription conversion time was 29 days, 17.482 hours.

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

### 5.5.1 Inadvertent Enrollment Deactivations [Metric 25]

There were no reports indentified of inadvertent enrollment deactivations.

### 5.5.2 Reports of False Positives [Metric 26]

A summary of two false positive reports (Report #3 and Report #4) are presented in Section 6.

### 5.5.3 Failure of Re-enrollment Notifications [Metric 27]

A total of 248 distinct prescribers were scheduled to receive re-enrollment reminders this reporting period. Overall, a total of 313 re-enrollment notification faxes were sent since program inception, including reminders. Of the 248 unique prescribers, 225 successfully received a fax notification for re-enrollment. There were a total of 23 unique physicians outstanding who have not had a successful re-enrollment notification received: 19 of the 23 had 1 fax attempt and 4 had 2 unsuccessful fax attempts.

### 5.5.4 Reports of False Negatives [Metric 28]

A summary of one false negative report System Error #11 is presented in Section 5.4.

## 5.6 Audits

No audits were conducted during the current reporting period.

### 5.6.1 Periodic Surveys of Stakeholders

No surveys of prescribers, inpatient pharmacists, or patients were planned or conducted during the current reporting period. Knowledge, Attitude, and, Behavior surveys will be conducted for the 12 months assessment report.

## 6 TIRF REMS Access Non-Compliance

During the current reporting period, instances of potential stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. The following is a list of resolved and pending potential reports of non-compliance.

| Report No. | Report Description | Report Status | Outcome/Resolution |
|---|---|---|---|
| 1 | Call Center reported: Office staff completing or initiating enrollment on prescriber's behalf without prescriber's knowledge. | Closed | Outreach was conducted with prescriber. Enrollment was deactivated at prescriber's request so enrollment could be re-initiated; the Knowledge Assessment was unsuspended to allow prescriber to re-take the assessment. The TIRF REMS Access program Call Center will track deactivation and Knowledge Assessment suspension in program database for reporting, as needed. |
| 2 | Call Center reported: Three examples of prescriber modification to attestation language on PPAF form for independent TIRF REMS program and TIRF REMS Access program PPAF (e.g., crossed out opioid tolerance confirmation and replaced with "Pt not on an around-the-clock med but has been using fentanyl without side effects for some time"; "my patient is intolerant of all opioid analgesics except TIRF medicines and understand this is an off-label use"). | Closed | In all cases, prescriber was contacted and advised the PPAF cannot be accepted with changes to the attestation language. The following information has been confirmed:<br>• Prescriber #1 – Resubmitted a new / clean PPAF with no language crossed out on the form, and patient received TIRF medicine.<br>• Prescriber #2 – Did not resubmit PPAF; however, a subsequent prescriber resubmitted a new/clean PPAF, and patient received TIRF medicine. This case will be referred to the NCRT for monitoring and potential future action.<br>• Prescriber #3 – No updated PPAF received; confirmed no prescription filled for the patient. |

(continued)

| Report No. | Report Description | Report Status | Outcome/Resolution |
|---|---|---|---|
| 3 | On 15 March 2012, it was discovered that an update was run that was originally developed for transition activities to move the data from independent TIRF REMS program to the TIRF REMS Access program. The update allowed 39 prescriber records to transition in an enrolled status into the TIRF REMS Access program in error. Of the 39 prescriber records enrolled in error, the TIRF REMS Access program identified that 10 prescriptions were authorized in error representing 6 unique prescriber records.<br><br>Root Cause: The Standard Operating Procedure (SOP) requires code review and updates to be run in test environment prior to release to production. Because this SOP contains wording that certain steps can be skipped if the update has been previously tested and validated, the developer did not perform these steps. However, because this update was used for a different purpose than it was originally tested for, it should have been treated and tested as a new update. | Closed | Enrollment records were voided, enrollment status was corrected in the TIRF REMS Access program system, a complete analysis was performed to determine the fills against the invalid records, and SOP clarifications and modifications were made. |
| 4 | A chain pharmacy was incorrectly flagged as having completed both their SOW and Vendor Verification and became enrolled. This chain had 102 associated stores. Of those 102 stores, some were marked as trained by the chain. As a result, there was one instance of a prescription authorized in error. Root cause: Inadequate process documented. | Closed | The chain pharmacy record was updated and 102 chain store records were corrected. The TIRF REMS Access program deleted all of the store enrollments. |

(continued)

| Report No. | Report Description | Report Status | Outcome/Resolution |
|---|---|---|---|
| 5 | System Error: On 21 March 2012, (b) (4) (a switch provider) discovered that NDC codes for Actiq and Fentora were not routing to TIRF REMS Access program and that claims processed during this time period for these medicines did not pass through all of the REMS edits prior to dispensing. As a result, there were 234 prescriptions that were not sent from (b) (4) to the TIRF REMS Access program for REMS edits from 12 March 2012 until 21 March 2012. It was discovered that (b) (4) had not put the correct start date (12 March 2012) for claims for these NDC codes to start routing to the TIRF REMS Access program. | Closed | (b) (4) corrected the issue within 24 hours of discovery and the NDC codes for these products were subsequently properly routed properly to the TIRF REMS Access program for the REMS edits.<br><br>Of the 234 claims affected during this time period, 155 would have successfully passed REMS edits if they had been properly routed through the TIRF REMS Access program. The remaining 79 claims would have been rejected: 11 due to both pharmacy and prescriber REMS edits, 25 due to pharmacy REMS edits, and 43 due to prescriber REMS edits. Educational outreach was conducted to the affected pharmacies and prescribers to the extent feasible. In the future, additional documentation will be requested from (b) (4) Quality Management to confirm proper processing of new NDC codes. |
| 6 | System Error: On 09 April 2012, (b) (4) discovered that claims for retail stores were not routed to the TIRF REMS Access program from 12 March 2012 until 09 April 2012 and claims for TIRF medicines did not pass through all of the REMS edits prior to dispensing. As a result, there were 11 prescription claims that did not pass through the REMS edits during this period. | Closed | (b) (4) corrected the issue on the same day (09 April 2012) and all subsequent claims were routed properly to the TIRF REMS Access program for REMS edits.<br><br>Of the 11 claims affected during this time period, 7 would have successfully passed the REMS edits if properly routed through the TIRF REMS Access program. The remaining 4 claims would have been rejected: 1 due to both pharmacy and prescriber REMS edits, and 3 due to prescriber REMS edits. Outreach was conducted to the affected pharmacies and prescribers to the extent feasible. As a result, (b) (4) instituted revised rules to limit ability to alter NDC routing for TIRF medicines. |

(continued)

| Report No. | Report Description | Report Status | Outcome/Resolution |
|---|---|---|---|
| 7 | System Error: On 27 March 2012, it was discovered that one TIRF program NDC code was incorrectly communicated to the switch providers (b) (4) and (b) (4) Claims for this NDC code sent through (b) (4) from 12 March 2012 until 27 March 2012 and from (b) (4) 12 March 2012 until 28 March 2012 were not routed to the TIRF REMS Access program and did not pass through all of the REMS edits prior to dispensing. As a result, there were 2 prescription claims that did not pass through all of the REMS edits prior to dispensing. | Closed | The error was corrected by (b) (4) on 27 March 2012 and by (b) (4) on 28 March 2012.<br><br>Both of these prescriptions would have been rejected due to prescriber REMS edits if properly routed through the TIRF REMS Access program. Outreach was conducted to the affected pharmacies and prescribers to the extent feasible. On 25 April, 2012, the TIRF REMS access program instituted a process to validate the correct NDC codes before providing to switch providers. |
| 8 | System Error: On 12 March 2012, (b) (4) stores were temporarily deactivated from the TIRF REMS Access program from 12:01AM EST until approximately 1:30AM EST to allow for customization of REMS rejection errors reported back to (b) (4) locations. During this window, one transaction was transmitted by an unenrolled (b) (4) location and, as a result, did not process through the TIRF REMS Access program.<br><br>The single prescription would have been rejected due to pharmacy not enrolled if properly routed. | Closed | On 12 March 2012, The TIRF REMS Access program conducted outreach and enrolled the (b) (4) pharmacy location in the TIRF REMS program. The enrollment was completed on 12 March 2012. After completion of the enrollment, the prescription claim was reversed and reprocessed through the REMS edits on 12 March 2012 where it successfully passed all REMS validation checks. (b) (4) confirmed that the patient received proper counseling upon dispensing of the medication. This instance occurred during the launch window for the TIRF REMS Access program. Future customization requirements will follow specific guidelines for change requests. |

(continued)

| Report No. | Report Description | Report Status | Outcome/Resolution |
|---|---|---|---|
| 9 | System Error:<br>On 05 April 2012, it was discovered that all transactions for TIRF medicines were not being routed to the TIRF REMS Access program. Upon investigation, it was discovered that data aggregators and pharmacy software vendors have direct connections to payers and do not require the usage of a traditional switch provider to send claims for payment. By not sending the claim through a traditional switch provider, the claim will not pass through the REMS edits prior to dispensing. | Closed | Beginning on 24 April 2012, the TIRF REMS Access program initiated outreach to all contracted vendors and data aggregators to identify those that have direct connections to payers that allow them to bypass a traditional switch network. As of the close of the reporting period, 2 vendors were identified as having direct connections to payers. One vendor confirmed that they are now sending all TIRF medicines to the TIRF REMS Access program. The TIRF REMS Access program is currently working with the second vendor to establish an amendment and to route all TIRF medicines to the TIRF REMS Access program for REMS edits.<br><br>The TIRF REMS Access program also requested that (b) (4) perform the same outreach to vendors and data aggregators that are directly connected to (b) (4) for traditional switching services. As of the close of this reporting period, (b) (4) has identified 1 data aggregator with direct connections to payers that require amendment. The data aggregator has confirmed that they are now sending all TIRF medicines to (b) (4) |
| 10 | Received pharmacist complaint regarding lack of weekend coverage at TIRF REMS Access program Call Center. Pharmacist reported that the prescriber for a prescription was unaware of PPAF requirement and that the patient was in pain. Pharmacist was unable to resolve rejected claim provided the patient with 3 tablets to carry the patient through the weekend. | Pending | There is no live coverage for the TIRF REMS Access program over the weekend. Stakeholders are able to leave a voice mail message after Call Center operation hours, including during the weekends. Live Call Center coverage is available Monday through Friday 8am-8pm EST. (The Call Center was not open seven days a week for independent TIRF REMS programs.) The TIRF REMS Access program Call Center will continue to monitor trends of calls and complaints. As part of standard procedures, this case was forwarded as an adverse event to the appropriate Sponsor for further research and follow up. Additional investigation is ongoing to confirm the “3 tablets dispensed” were a TIRF medicine. |

(continued)

| Report No. | Report Description | Report Status | Outcome/Resolution |
|---|---|---|---|
| 11 | Two scenarios reported where the Pharmacist submitted original claim and received a reject for "prescriber not enrolled." The Pharmacist re-submitted the claim for the same prescription with prescriber that was enrolled. Prescribers were not in the same facility. Prescriber requesting that patient be disassociated from his profile. | Closed | Outreached to Pharmacist in charge to discuss data submitted on paid claim. Pharmacist in charge at (b) (4) store did not want patient to experience withdrawal symptoms so the prescription was switched to a Prescriber that was enrolled. Patient has since switched to another medication. All prescribers involved were contacted. This case will be referred to the NCRT for monitoring and potential future action. On 5/24/12, (b) (4) provided the following response to this issue: "This is an isolated situation and the store has received education on the proper procedures for handling TIRF REMS medications. The patient is seeing a doctor now who is enrolled in the program." |

Source: Data on file.

# 7 SAFETY SURVEILLANCE

## 7.1 Adverse Events

During the current reporting period, an analysis of the FDA AERS reporting database released in the fourth quarter of 2011 did not identify any reports that met the inclusion criteria for the TIRF REMS Access program Assessment Report. Data for the first quarter of 2012 was not available at the time of this report.

## 7.2 American Association of Poison Control Centers (AAPCC)

The AAPCC database is monitored to identify reports of misuse, abuse, and overdose. The AAPCC database includes all 57 poison centers in the US. Reports were requested from AAPCC on calls related to the aggregated data for the class of immediate-release transmucosal fentanyls (no manufacturer names or brand names are provided). The search also included reports of unknown manufacturer oral immediate release fentanyl products, and "unknown fentanyls" with oral and/or inhalation/nasal route(s) of exposure. AAPCC listings of reports for TIRF medicines and unknown fentanyl are presented in Appendix 11.2. In future reports, data will be compared across reporting periods.

The AAPCC received reports for 9 cases of known exposure to oral fentanyl immediate-release medicines during the current reporting period. The 9 cases had medical outcomes of 1 major effect, 1 moderate effect, 5 minor effects, 1 unable to follow/judged as potentially toxic exposure, and 1 not followed/judged as non toxic exposure. "Effect" is defined as sign,

symptom, or laboratory abnormality and described as minor, moderate, major, or death (See Appendix 11.2 for effect definitions).

Eight cases of exposure to unknown fentanyl were reported to the AAPCC during the current reporting period. The cases had medical outcomes of 1 death (indirect report), 2 major effects, 1 moderate effect, 3 unable to follow/judged as potentially toxic exposure, and 1 not followed/minimal clinical effect possible.

The following tables (Tables 17-24) include reports for exposures to TIRF medicines received between 28 December 2011 and 27 April 2012. The tables do not include reports for unknown fentanyls.

***Human Exposure Cases: Site of Call/Site of Exposure***

As shown in Table 17, of the 9 human exposures associated with TIRF medicines reported, 4 call sites were from a residence (own or other) but there were 8 cases where the site of exposure actually occurred at a residence (own or other). Another 4 calls were made from a health care facility and 1 from "other." Beyond residences, 1 exposure occurred in a public area.

**Table 17: Site of Call and Site of Exposure, Human Exposure Cases Associated with TIRF Medicines: 28 December 2011 to 27 April 2012**

| Site | Site of Caller Case Count | Site of Exposure Case Count |
|---|---|---|
| Health Care Facility | 4 | 0 |
| Other | 1 | 0 |
| Other Residence | 0 | 0 |
| Own Residence | 4 | 8 |
| Public Area | 0 | 1 |
| Restaurant/food service | 0 | 0 |
| School | 0 | 0 |
| Unknown | 0 | 0 |
| Workplace | 0 | 0 |
| **Total** | **9** | **9** |

Source: AAPCC Database Table 2.

***Human Exposure Cases: Age and Gender Distribution***

The age and gender distribution of human exposures associated with TIRF medicines is outlined in Table 18. Children <2 years of age were involved in 3 exposures. Another 6 exposures were reported in adults ≥20 years of age.

**Table 18: Age and Gender Distribution of Human Exposures Associated with TIRF Medicines: 28 December 2011 to 27 April 2012**

| Age (yr) | Male | Female | Unknown | Total |
|---|---|---|---|---|
| 1 | 1 | 1 | 0 | 2 |
| 2 | 0 | 1 | 0 | 1 |
| 3-19 | 0 | 0 | 0 | 0 |
| 20-29 | 1 | 1 | 0 | 2 |
| 30-39 | 1 | 0 | 0 | 1 |
| 40-49 | 0 | 2 | 0 | 2 |
| 50-59 | 0 | 0 | 0 | 0 |
| 60-69 | 1 | 0 | 0 | 1 |
| **Total** | **4** | **5** | **0** | **9** |

Source: AAPCC Database Table 3A.

***All fatalities – All Ages and Gender***

No fatalities were reported in the AAPCC data associated with TIRF medicines (AAPCC Database Table 4). There was one fatality reported for exposure to an unknown fentanyl product.

***Human Exposure Cases: Number of Substances***

As shown in Table 19, a single substance was implicated in 6 reported human exposures, and 3 patients were exposed to two or more drugs or products. There were no exposure- related fatalities. For cases that involved multiple substances, the route of exposure is only captured for one of the substances; therefore, the reported case may include fentanyls that are not oral or inhalation formulations and may not be limited to the class of immediate-release fentanyls.

**Table 19: Number of Substances Involved in Human Exposure Cases Associated with TIRF Medicines or a Fentanyl and included Oral Inhalation Route of Exposure: 28 December 2011 to 27 April 2012**

| Number of Substances | Case Count | Fatality Case Count |
|---|---|---|
| 1 | 6 | 0 |
| 2 | 1 | 0 |
| 3 | 1 | 0 |
| 4 | 0 | 0 |
| 5 | 1 | 0 |
| **Total** | **9** | **0** |

Source: AAPCC Database Table 5.

***Reason for Exposure***

The reasons for both unintentional (general and misuse) and intentional (abuse, suspected suicide, and unknown) human exposures associated with TIRF medicines are shown in Table 20.

**Table 20: Reason for Human Exposure Cases Associated with TIRF Medicines: 28 December 2011 to 27 April 2012**

| Reason Category | Case Count |
|---|---|
| Unintentional | |
| Unintentional General | 3 |
| Unintentional Misuse | 1 |
| Intentional | |
| Intentional Abuse | 2 |
| Intentional Suspected Suicide | 2 |
| Intentional Unknown | 1 |
| **Total** | **9** |

Source: AAPCC Database Table 6A.

***Therapeutic Errors***

There were no reports of therapeutic errors associated with TIRF medicines in the current reporting period (AAPCC Database Table 6B).

***Reason of Exposure by Age***

Intentional and unintentional exposures by age are shown in Table 21. Adults >19 years of age accounted for 6 human exposures, 5 intentional and 1 unintentional. There were 3 unintentional exposures in children <6 years of age.

**Table 21: Distribution of Reason for Exposure by Age Associated with TIRF Medicines: 28 December 2011 to 27 April 2012**

| Reason | <6 | 6-12 | 13-19 | >19 | Unknown | Unknown Child | Unknown Adult | Missing |
|---|---|---|---|---|---|---|---|---|
| Unintentional | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Intentional | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| **Total** | **3** | **0** | **0** | **6** | **0** | **0** | **0** | **0** |

Source: AAPCC Database Table 7.

***Reason of Exposure by Age for Fatalities***

There were no reports of unintentional fatalities from exposure to TIRF medicines (AAPCC Database Table 8).

***Route of Exposure***

Ingestion was the route of exposure in 7 of 9 cases associated with TIRF medicines (Table 22), followed in frequency by parenteral (n=1) and dermal (n=1). Each exposure case may have more than one route

**Table 22: Route of Exposure for Human Exposure Cases: 28 December 2011 to 27 April 2012**

| Route | Human Exposures | Fatal Exposures |
|---|---|---|
| Ingestion | 7 | 0 |
| Parenteral | 1 | 0 |
| Dermal | 1 | 0 |
| **Total** | **9** | **0** |

Source: AAPCC Database Table 9.

***Medical Outcome***

Table 23 displays the medical outcome of human exposure cases associated with TIRF medicines distributed by age. A greater number of severe medical outcomes was observed in the older age groups.

**Table 23: Medical Outcome of Human Exposure Cases by Patient Age: 28 December 2011 to 27 April 2012**

| Outcome | <6 yr | 6-12 yr | 13-19 yr | >19 | Unknown Child | Unknown Adult |
|---|---|---|---|---|---|---|
| No effect | 0 | 0 | 0 | 0 | 0 | 0 |
| Minor effect | 1 | 0 | 0 | 4 | 0 | 0 |
| Moderate effect | 1 | 0 | 0 | 0 | 0 | 0 |
| Major effect | 0 | 0 | 0 | 1 | 0 | 0 |
| Death | 0 | 0 | 0 | 0 | 0 | 0 |
| No follow-up, nontoxic | 1 | 0 | 0 | 0 | 0 | 0 |
| No follow-up, minimal toxicity | 0 | 0 | 0 | 0 | 0 | 0 |
| No follow-up, potentially toxic | 0 | 0 | 0 | 1 | 0 | 0 |
| Unrelated effect | 0 | 0 | 0 | 0 | 0 | 0 |
| Confirmed nonexposure | 0 | 0 | 0 | 0 | 0 | 0 |
| Death, indirect report | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **3** | **0** | **0** | **6** | **0** | **0** |

Source: AAPCC Database Table 11.

Table 24 compares medical outcome and reason for exposure and shows a comparable frequency of serious outcomes in intentional (n=5) versus unintentional exposures (n=4).

**Table 24: Medical Outcome by Reason for Exposure in Human Exposures[a]: 28 December 2011 to 27 April 2012**

| Outcome | Unintentional | Intentional |
|---|---|---|
| Death | 0 | 0 |
| Death, indirect report | 0 | 0 |
| Major effect | 0 | 1 |
| Minor effect | 2 | 3 |
| Moderate effect | 1 | 0 |
| No effect | 0 | 0 |
| No follow-up, nontoxic | 1 | 0 |
| No follow-up, minimal toxicity | 0 | 0 |
| No follow-up, potentially toxic | 0 | 1 |
| Unrelated effect | 0 | 0 |
| **Total** | 4 | 5 |

Source: AAPCC Database Table 12.

## 8 FDA COMMUNICATIONS

FDA communicated with TRIG on 16 March 2012 regarding consumer inquiries about long phone hold times when contacting the TRIG Access program Call Center. Metrics regarding call volume and operations were provided to the agency on 16 March 2012, and the proposed action plan was implemented by 23 March 2012. (See System Error #4, Section 5.4 for additional details.)

FDA requested information on the geographic distribution of pharmacies enrolled in the TIRF REMS Access program in the Kansas City, MO metropolitan area because the agency received a complaint from a prescriber that the two pharmacies in his/her local area were not enrolled. On 08 May 2012, the TIRF REMS Access program responded that there were enrolled pharmacies in the area in question. FDA acknowledged that the pharmacies within this area may have been enrolled in the TIRF REMS Access program but that pharmacy staff may not have been educated on the program or aware that their pharmacy was enrolled.

## 9 POST-APPROVAL STUDIES AND CLINICAL TRIALS

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

# 10 OVERALL CONCLUSIONS

The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval. Prescribers, patients, and pharmacies were transitioned from independent TIRF REMS programs and, subsequent to 12 March and through the end of this reporting period, many additional stakeholders successfully enrolled in the TIRF REMS Access program.

The REMS goal of educating prescribers and pharmacists on the potential for misuse, abuse, addiction, and overdose is being documented through the implementation of the Knowledge Assessment, which is required for enrollment. Patient education is completed through the PPAFs, and most PPAFs received within this reporting period were within the required time frame.

With an overall volume of more than 14,000 prescriptions authorized for REMS edits, there were few reports of patients unable to gain access to TIRF medicines or reports of system issues. The TIRF REMS Access program system continues to be monitored for issues and, where appropriate, corrective actions instituted. Only a few instances of un-enrolled physicians prescribing TIRF medicines, un-enrolled pharmacies dispensing, and un-enrolled patients receiving product were identified. A thorough investigation is applied to all of these instances, and, where complete, corrective actions have been documented. Sponsors remain vigilant in monitoring spontaneous reports and external data sources, such as AAPCC, to identify safety risks.

Surveillance methods using FDA AERS and AAPCC data identified few exposures. There were three pediatric exposures reported in AAPCC data for TIRF medicines, including one minor effect, one moderate effect, and one no follow-up/non toxic effect. There were no fatalities reported for exposure to TIRF medicines. There was one fatality reported for exposure to an unknown fentanyl.

Over all, the TIRF REMS Access program has adequately addressed its goals for the current reporting period.

# 11 APPENDICES

## 11.1 Medical Dictionary for Drug Regulatory Activities (MedDRA) Preferred Terms

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

| Primary SOC | High Level Group | High Level Term | Preferred Term |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | Respiratory disorders NEC | Breathing abnormalities | Cardio respiratory arrest |
| Cardiac disorders | Cardiac arrhythmias | Ventricular arrhythmias and cardiac arrest | Cardiac arrest |
| Respiratory, thoracic and mediastinal disorders | Respiratory disorders NEC | Breathing abnormalities | Respiratory arrest |
| **Misuse** | | | |
| Psychiatric disorders | Psychiatric disorders NEC | Substance-related disorders | Intentional drug misuse |
| Drug abuse dependence and withdrawal SMQ (Standardized MedDRA Query) | | | |
| **Abuse** | | | |
| Psychiatric disorders | Psychiatric disorders NEC | Substance-related disorders | Drug abuse |
| Social circumstances | Lifestyle issues | Drug and chemical abuse | Drug abuser |
| Psychiatric disorders | Psychiatric disorders NEC | Substance-related disorders | Substance abuse |
| Social circumstances | Lifestyle issues | Drug and chemical abuse | Substance abuser |
| Social circumstances | Lifestyle issues | Drug and chemical abuse | Ex-drug abuser |
| Drug abuse dependence and withdrawal SMQ (Standardized MedDRA Query) | | | |
| **Inappropriate** | | | |
| Injury, poisoning and procedural complications | Medication errors | Maladministrations | Drug administered at inappropriate site |
| Injury, poisoning and procedural complications | Medication errors | Maladministrations | Inappropriate schedule of drug administration |
| Surgical and medical procedures | Therapeutic procedures and supportive care | Therapeutic procedures NEC | Off label use |
| Injury, poisoning and procedural complications | Medication errors | Maladministrations | Drug administered to patient of inappropriate age |
| **Medication Error** | | | |
| Injury, poisoning and procedural complications | Medication errors | Medication errors NEC | Intercepted medication error |
| Injury, poisoning and procedural complications | Medication errors | Medication errors NEC | Medication error |
| Injury poisoning and procedural complications | Medication errors | Maladministrations | Counterfeit drug administered |
| Injury, poisoning and procedural complications | Medication errors | Maladministrations | Drug administration error |
| Injury, poisoning and procedural complications | Medication errors | Maladministrations | Drug dose omission |

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

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

## 11.2 AAPCC LISTINGS

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

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

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

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

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

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

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

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

Listing of TRIG TIRF Immediate-Release Medicines

| Subject | Start Date | Public Case Number | Age | Gender | Substance Rank | No of Substances | Formulation | Quantity | Quantity Unit | Major Category | Reason For Exposure | Medical Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1/1/12 | 9983173722012 | 22 | Male | 1 | 2 | Solid (tablets / capsules / caplets) | 14 | tabs / pills / capsules | Fentanyl | Intentional - Unknown | Minor effect |
| | 1/1/12 | 9983173722012 | 22 | Male | 2 | 2 | Solid (tablets / capsules / caplets) | 2 | tabs / pills / capsules | Benzodiazepines | Intentional - Unknown | Minor effect |
| 2 | 1/2/12 | 30122033582012 | 30 | Male | 1 | 1 | Liquid | NULL | Unknown | Fentanyl | Intentional - Abuse | Major effect |
| 3 | 1/17/12 | 1407423672012 | 49 | Female | 5 | 5 | Solid (tablets / capsules / caplets) | 275 | mcg | Fentanyl | Intentional - Suspected suicide | Minor effect |
| | 1/17/12 | 1407423672012 | 49 | Female | 1 | 5 | Solid (tablets / capsules / caplets) | 30 | tabs / pills / capsules | Other Types of Sedative/Hypnotic/ Anti-Anxiety or Anti-Psychotic Drug | Intentional - Suspected suicide | Minor effect |
| | 1/17/12 | 1407423672012 | 49 | Female | 2 | 5 | Solid (tablets / capsules / caplets) | 2 | tabs / pills / capsules | Carisoprodol (Formulated Alone) | Intentional - Suspected suicide | Minor effect |
| | 1/17/12 | 1407423672012 | 49 | Female | 3 | 5 | Solid (tablets / capsules / caplets) | 2 | tabs / pills / capsules | Acetaminophen with Hydrocodone | Intentional - Suspected suicide | Minor effect |
| | 1/17/12 | 1407423672012 | 49 | Female | 4 | 5 | Solid (tablets / capsules / caplets) | 45 | tabs / pills / capsules | Acetaminophen with Oxycodone | Intentional - Suspected suicide | Minor effect |
| 4 | 1/18/12 | 20124953322012 | 21 | Female | 1 | 1 | Solid (tablets / capsules / caplets) | 600 | mg | Fentanyl | Intentional - Abuse | Unable to follow, judged as a potentially toxic exposure |
| 5 | 2/22/12 | 3409573352012 | 14 | Female | 1 | 1 | Other | NULL | Unknown | Fentanyl | Unintentional - General | Moderate effect |
| 6 | 3/11/12 | 17653713532012 | 66 | Male | 1 | 3 | Solid (tablets / capsules / caplets) | 1.2 | mg | Fentanyl | Intentional - Suspected suicide | Minor effect |
| | 3/11/12 | 17653713532012 | 66 | Male | 2 | 3 | Solid (tablets / capsules / caplets) | 120 | mg | Oxycodone Alone or in Combination (Excluding Combination Products with Acetaminophen or Acetylsalicylic Acid) | Intentional - Suspected suicide | Minor effect |
| | 3/11/12 | 17653713532012 | 66 | Male | 3 | 3 | Solid (tablets / capsules / caplets) | 20 | mg | Methadone | Intentional - Suspected suicide | Minor effect |
| 7 | 3/17/12 | 26199563612012 | 45 | Female | 1 | 1 | Patch | 1 | taste / lick / drop | Fentanyl | Unintentional - Misuse | Minor effect |
| 8 | 4/6/12 | 18509453282012 | 20 | Male | 1 | 1 | Solid (tablets / capsules / caplets) | NULL | Unknown | Fentanyl | Unintentional - General | Minor effect |
| 9 | 4/13/12 | 728291893052012 | 2 | Female | 1 | 1 | Other | 1 | taste / lick / drop | Fentanyl | Unintentional - General | Not followed, judged as nontoxic exposure (clinical effects not expected) |

Listing of TRIG TIRF Immediate-Release Medicines

| Subject | Start Date | Public Case Number | Age | Gender | Substance Rank | No of Substances | Formulation | Quantity | Quantity Unit | Major Category | Reason For Exposure | Medical Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1/15/12 | 23666153092012 | 25 | Male | 1 | 1 | Patch | 1 | each (e.g. bites / stings) | Fentanyl | Intentional - Unknown | Unable to follow, judged as a potentially toxic exposure |
| 2 | 2/15/12 | 7896563442012 | NULL | Female | 1 | 3 | Solid (tablets / capsules / caplets) | 5 | tabs / pills / capsules | Acetaminophen with Oxycodone | Intentional - Misuse | Not followed, minimal clinical effects possible (no more than minor effect possible) |
| | 2/15/12 | 7896563442012 | NULL | Female | 2 | 3 | Solid (tablets / capsules / caplets) | 1 | tabs / pills / capsules | Methadone | Intentional - Misuse | Not followed, minimal clinical effects possible (no more than minor effect possible) |
| | 2/15/12 | 7896563442012 | NULL | Female | 3 | 3 | Other | 2 | each (e.g. bites / stings) | Fentanyl | Intentional - Misuse | Not followed, minimal clinical effects possible (no more than minor effect possible) |
| 3 | 3/2/12 | 19455103222012 | NULL | Male | 1 | 1 | Solid (tablets / capsules / caplets) | NULL | Unknown | Fentanyl | Intentional - Abuse | Unable to follow, judged as a potentially toxic exposure |
| 4 | 3/16/12 | 5079873332012 | 37 | Female | 1 | 1 | Patch | NULL | Unknown | Fentanyl | Intentional - Suspected suicide | Major effect |
| 5 | 3/18/12 | 207522223752012 | 30 | Male | 1 | 1 | Solid (tablets / capsules / caplets) | 2 | each (e.g. bites / stings) | Fentanyl | Intentional - Suspected suicide | Unable to follow, judged as a potentially toxic exposure |
| 6 | 3/28/12 | 4109423642012 | 36 | Male | 1 | 4 | Cream / lotion / gel | NULL | Unknown | Fentanyl | Intentional - Abuse | Death, indirect report |
| | 3/28/12 | 4109423642012 | 36 | Male | 2 | 4 | Solid (tablets / capsules / caplets) | NULL | Unknown | Benzodiazepines | Intentional - Abuse | Death, indirect report |
| | 3/28/12 | 4109423642012 | 36 | Male | 3 | 4 | Unknown | NULL | Unknown | Cocaine | Intentional - Abuse | Death, indirect report |
| | 3/28/12 | 4109423642012 | 36 | Male | 4 | 4 | Solid (tablets / capsules / caplets) | NULL | Unknown | Benzodiazepines | Intentional - Abuse | Death, indirect report |
| 7 | 4/14/12 | 30352563582012 | 21 | Female | 1 | 4 | Powder / granules | NULL | Unknown | Fentanyl | Intentional - Suspected suicide | Major effect |
| | 4/14/12 | 30352563582012 | 21 | Female | 2 | 4 | Solid (tablets / capsules / caplets) | NULL | Unknown | Hydromorphone | Intentional - Suspected suicide | Major effect |
| | 4/14/12 | 30352563582012 | 21 | Female | 3 | 4 | Solid (tablets / capsules / caplets) | NULL | Unknown | Other Types of Sedative/Hypnotic/ Anti-Anxiety or Anti-Psychotic Drug | Intentional - Suspected suicide | Major effect |
| | 4/14/12 | 30352563582012 | 21 | Female | 4 | 4 | Solid (tablets / capsules / caplets) | NULL | Unknown | Benzodiazepines | Intentional - Suspected suicide | Major effect |
| 8 | 4/18/12 | 10170303722012 | 34 | Female | 1 | 3 | Solid (tablets / capsules / caplets) | NULL | Unknown | Hydromorphone | Intentional - Suspected suicide | Moderate effect |