ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSARM) BRIEFING BOOK

FOR THE

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

August 3, 2018

TIRF REMS Industry Group (TRIG) of Companies:

BioDelivery Sciences International, Inc.

Insys Therapeutics, Inc.

SpecGX LLC (a wholly owned subsidiary of Mallinckrodt Inc.)

Mylan, Inc.

Par Pharmaceutical, Inc.

Sentynl Therapeutics, Inc.

Teva Pharmaceuticals USA, Inc.

West Therapeutic Development, LLC

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
BTCP	Breakthrough Cancer Pain
CAP	Corrective Action Plan
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DEA	Drug Enforcement Administration
DIM	Drug Involved Mortality
DOB	Date of Birth
ED	Emergency Department
ER	Extended-Release
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
ID	Identification
IMF	Illicitly Manufactured Fentanyl
IR	Immediate Release
KAB	Knowledge, Attitude, and Behavior
LRx	Longitudinal prescription database
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCCN	National Comprehensive Clinical Practice
NCRT	Non-Compliance Review Team
NFLIS	National Forensic Laboratory Information System
PPAF	Patient-Prescriber Agreement Form
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
REMS edits	Checks conducted by the TIRF REMS Access Program to confirm that all safety requirements were met
TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl product(s)
TIRF REMS Access Program	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/USA	United States/United States of America

1. OVERVIEW

1.1. Introduction

Transmucosal Immediate-Release Fentanyl (TIRF) medications are indicated for the management of breakthrough pain in cancer patients 18 years of age (16 for Actiq and generic equivalents) and older who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer.

Fentanyl is a potent, synthetic, μ-opioid receptor agonist with high lipid solubility, a rapid onset of action, and a short duration of effect. The TIRF products were developed to address the previously unmet need of cancer patients suffering breakthrough cancer pain (BTCP). The TIRF products are the only medications that have an indication for the treatment of BTCP, and BTCP is the only indication the TIRF products have. For appropriately identified cancer patients, TIRF products relieve BTCP and can improve quality of life, with the benefits of treating this debilitating pain outweighing the serious risks associated with fentanyl.

The Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program is a shared system REMS approved by the Food and Drug Administration (FDA) on 28 December 2011 and launched on 12 March 2012. This program was the first opioid class-wide REMS.

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

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

The REMS program is sponsored by the TIRF REMS Industry Group (TRIG), which includes BioDelivery Sciences International, Inc., Insys Therapeutics, Inc., SpecGX LLC (a wholly owned subsidiary of Mallinckrodt Inc.), Mylan, Inc., Par Pharmaceutical, Inc., Sentynl Therapeutics, Inc., Teva Pharmaceuticals USA, Inc., and West Therapeutic Development, LLC.

The TIRF medicines subject to the TIRF REMS are shown in Table 1.

Table 1: TIRF Products Included in the REMS

Product Name	Dosage Form
Abstral® (fentanyl citrate) and generic	sublingual tablets
Actiq® (fentanyl citrate) and generics	oral transmucosal lozenge
Fentora® (fentanyl citrate) and generic	buccal tablet
Lazanda® (fentanyl citrate)	nasal spray
Onsolis® (fentanyl citrate)	buccal soluble film
Subsys® (fentanyl)	sublingual spray

The TIRF REMS Access Program seeks to ensure that appropriately identified patients receive the medicines they need as safely as possible without undue burden. It was created so that informed risk-benefit decisions are made before initiating treatment with a TIRF and, while patients are treated, to ensure understanding of appropriate use. The REMS program helps to educate physicians and pharmacists on proper prescribing and monitoring and supports informed discussions with patients so that they understand the risks associated with the use of TIRF products.

Since its inception, the TIRF REMS Access Program has been an evolving collaborative initiative with FDA. As part of the FDA-approved REMS, the TRIG sponsors conduct ongoing monitoring and assessment of the program, submit periodic scheduled reports of their findings, and receive and act upon feedback and recommendations from the Agency. As a result, the TIRF REMS Access Program undergoes continual improvement in response to evidence-based review.

In the context of an evolving global opioid crisis, the TIRF REMS Access Program is responsive to changing expectations and medical practice regarding opioid use. Over the course of the program, the number of patients receiving TIRF medicines and the total number of TIRF prescriptions have declined sharply. The number of adverse events (AEs) of interest, such as overdose, death, addiction, and pediatric exposure associated with TIRF products, is very low, according to surveillance data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System.

Overall, and as set forth more fully in Section 1.7, the TIRF REMS Access Program is generally meeting its defined goals of mitigating the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. The TRIG is proposing improvements in specific areas of education and monitoring, which will be discussed in this document. In assessing the value and success of this evolving program, it is important to balance general opioid safety concerns with the important medical need of a defined patient population for access to TIRF medicines.

1.2. Clinical Context

1.2.1. Breakthrough Cancer Pain

Approximately 30–40% of patients with cancer present with pain at the time of diagnosis; this proportion increases up to 90% in advanced stages [Chang 2015]. Opioids, such as morphine, are

the mainstay maintenance treatment of chronic cancer-related pain [Janknegt 2018; Smith 2012]. However, between one third and two thirds of cancer patients treated with opioids still experience episodes of severe and debilitating BTCP [Smith 2012].

BTCP may result from the patient's disease, treatment, or other factors that damage the nervous system (i.e., neuropathic pain) or cause injury outside the nervous system (i.e., nociceptive pain) [Janknegt 2018; Smith 2012]. BTCP is episodic and characterized by a rapid onset and short duration [Smith 2012]. In a recent study [Davies 2013], 1,000 patients with BTCP experienced a median of 3 episodes per day, with the pain reaching peak intensity after a median of 5–10 minutes and lasting approximately 1 hour. The great majority of patients in this and other studies report that their pain is severe enough to interfere with daily activities, mood, and enjoyment of life [Smith 2012]. Even with the great suffering and debility that it can cause, BTCP is often undertreated [Smith 2012].

BTCP is typically treated with opioids, optimally with a fast-acting opioid matched with a short duration that matches the profile of the BTCP episode [Bennett 2005, Smith 2012]. Incident pain associated with an activity such as physical therapy or a medical procedure may be predictable and of sufficient duration that treatment with a short-acting opioid would be more appropriate [Chang 2015]. Oral short-acting opioids usually have an onset of action within 30–90 minutes and a duration of effect of 3–6 hours. End-of-dose pain that occurs as blood levels of the maintenance analgesic decline prior to the next dose may be best treated by adjusting the dose or timing of the maintenance therapy. However, BTCP, which is unpredictable and of shorter duration, is best treated with a TIRF product that has a more rapid onset of action and a shorter duration of effect, better matching idiopathic/spontaneous and unpredictable incident pain. TIRF products have an onset of action as soon as 5 minutes (average of 5-30 minutes across products) and an effective duration of 60-90 minutes [Mercadante 2015, Mercadante 2016]. Most TIRF products offer additional clinical advantages because they avoid first-pass hepatic metabolism and intestinal digestion [Simon 2014] and because fentanyl has a high potency (90–100× that of morphine) and minimal risk of cardiovascular AEs [Chang 2015, Stanley 2014].

The TIRF products are well matched to treat the rapid onset, high intensity, and short duration of BTCP. They are better suited to the treatment of unpredictable, intense, rapid onset BTCP than other opioids with longer onsets of actions and durations of effect. Because TIRFs can manage the BTCP effectively without requiring an increase of the dosage of the maintenance analgesic, they can also decrease the risks associated with unwarranted dosage increases [Simon 2014, Vellucci1 2016].

1.2.2. TIRF Products for Breakthrough Cancer Pain

Intravenous fentanyl was introduced in Europe in 1963 and in the US in 1968. Over the last 20 years, TIRF products that can be administered via buccal, sublingual, or intranasal routes have been developed to treat BTCP [Stanley 2014].

The use of BTCP treatments is influenced by patient-centric factors, such as underlying disease characteristics, patient preferences, and ease of administration. The available formulations of TIRF products can be prescribed according to these patient-specific needs, which should serve to improve the clinical response [Smith 2012]. TIRF products are particularly advantageous for the management of BTCP in outpatients and in patients who cannot tolerate oral medications, which may include up to 70% of cancer patients near the end of their life [Chang 2015].

Opioid medicines, including TIRF products, are an important component of pain management for certain patients, but they pose serious risks when used improperly. Like other opioids, high doses of fentanyl can lead to potentially life-threatening central nervous system effects, including sedation, respiratory depression, bradycardia, and unconsciousness [Stanley 2014]. TIRF medicines should be administered only to patients who are already opioid-tolerant based on around-the-clock opioid therapy. Patients considered opioid-tolerant are those who are taking for at least 1 week any of the following: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, 60 mg oral hydrocodone/day, or an equianalgesic dose of another oral opioid daily. (Around-the-clock opioid therapy does not necessarily imply the use of extended-release or long-acting opioids.)

Patients must remain on around-the-clock opioids when taking a TIRF medicine. TIRF therapy should not be initiated in patients who are naïve to around-the-clock opioid therapy, and TIRF therapy should be discontinued if patients discontinue their around-the-clock opioid therapy following instructions from their prescriber.

Ultimately, the decision to prescribe a TIRF product is a medical judgment based on the benefits and risks for each individual patient and informed by proper training provided through the TIRF REMS Access Program. When used properly, TIRF medicines can quickly and effectively control severe, rapid-onset pain that would otherwise be disabling [Gordon 2005].

However, given the risks of fentanyl, it remains a patient safety and public health priority to ensure appropriate prescribing; minimize abuse, misuse, and diversion; and prevent accidental exposure, especially in children. The TIRF REMS Access Program is intended to help balance the known risks with appropriate patient access to the TIRF medicines.

Physicians and pharmacists must be educated on appropriate use and prescribing, but they should also be able to maintain compliance with REMS requirements with minimal impact on patient care. If requirements become too burdensome, prescribers may not participate in the program, which could lead to increased prescribing of non-TIRF opioids that are less effective, making it difficult for patients to have appropriate and effective treatment of their BTCP [Nelson 2014].

1.3. Public Health Perspective

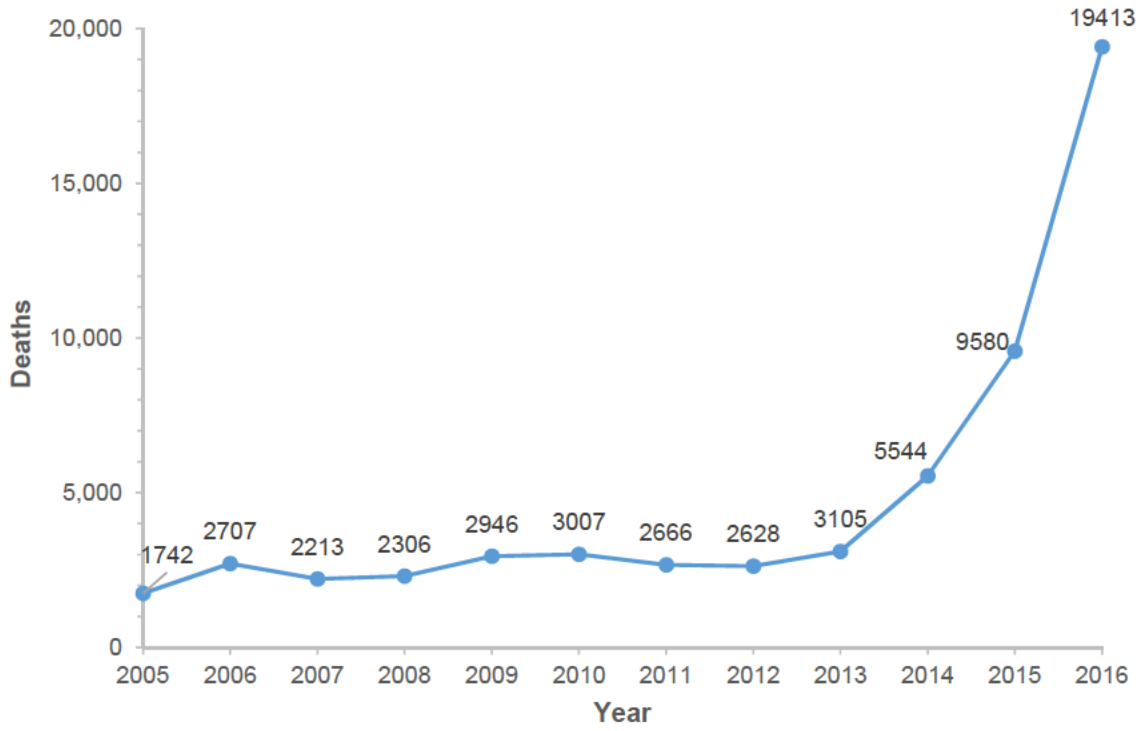
Effective management of BTCP achieves public health benefits. First and foremost, TIRF products relieve the burden of the intense and debilitating BTCP that a substantial number of cancer patients experience. They are the only medications that have an indication for this type of pain. By managing BTCP with the most appropriate therapy, treating physicians may avoid using increased doses of maintenance analgesics or the unnecessary use of short-acting opioids. Further, the TIRF products are indicated only for the treatment of BTCP and are available only through the TIRF REMS Access Program. The TIRF REMS includes mandatory participation and mandatory education for prescribers, pharmacists, and patients. The TIRF products are also subject to controlled prescribing, distribution, and dispensing, which further mitigate the risks associated with their use.

Fentanyl is a factor in the opioid crisis; however, the majority of cases of abuse, overdose, and death related to fentanyl result from the use of illicitly manufactured fentanyl (IMF) and fentanyl derivatives [DEA 2016a, United States Senate 2018]. The popular perception of the opioid crisis,

including media coverage, often fails to distinguish between the use of FDA-approved products and illicitly manufactured products. The main driver of the crisis today is the abuse of illicitly produced synthetic opioids, including and especially fentanyl [DEA 2018, Wolff 2018, O'Donnell 2017]. Synthetic opioids comprise a range of narcotic drugs designed and produced in the laboratory; examples include methadone, buprenorphine, fentanyl, and fentanyl derivatives.

According to the Centers for Disease Control and Prevention (CDC), deaths associated with synthetic opioids have increased by more than 500% in the past few years—from approximately 3,000 annually prior to 2014 to nearly 20,000 in 2016 (Figure 1) [DEA 2018].

Figure 1: Synthetic Opioid (FDA-approved and Illicit) Drug Poisoning Deaths in the US Between 2005–2016



Source: U.S. Drug Enforcement Administration (DEA) Intelligence Brief (May 2018).

Testing of drug samples containing fentanyl can distinguish between pharmaceutical and illicitly manufactured non-pharmaceutical fentanyl. However, testing of biologic samples (e.g., serum) cannot distinguish between pharmaceutical and non-pharmaceutical fentanyl. Therefore, it is not usually possible to determine from postmortem toxicology whether the fentanyl was manufactured pharmaceutically (e.g., fentanyl patches or TIRF products) or illicitly [Warner 2016].

The number of fentanyl prescriptions in the US has been relatively constant or has decreased during the same time period when fentanyl overdose deaths have increased dramatically [DEA 2016b, Gladden 2016, Warner 2016]. The Drug Enforcement Administration (DEA) has reported that the vast majority (in terms of quantity and proportion) of seizures of fentanyl involve illicitly produced fentanyl in powder form that has been smuggled into the US from

China or Mexico, rather than pharmaceutical formulations. Although pharmaceutical fentanyl is diverted for abuse in the US, DEA has stated that the relatively small-scale quantities of pharmaceutical fentanyl being diverted compared to the kilogram seizures of illicitly produced fentanyl indicate that illicitly-produced fentanyl is responsible for the current fentanyl epidemic in the US [DEA 2017]. In addition, as part of illicit production, fentanyl is often mixed with heroin and other substances (such as cocaine and methamphetamine) or used in counterfeit pharmaceutical prescription drugs. Consequently, users who buy these substances on the illicit market are often unaware of the specific substance they are consuming and the associated risk [Federal Register 2018].

TIRF medicines represent a small percentage (0.099%, calculated from IQVIA™ and REMS program data) of fentanyl prescriptions in the US, and the annual reporting of the TIRF REMS Access Program shows that the prescription volume has declined steadily since 2014. TIRF products are not significant contributors to the opioid crisis, nor are they responsible for the mounting toll of overdose and death caused by illicit fentanyl and fentanyl-related substances (structural analogues). There are, however, important potential risks associated with their use, misuse, and accidental exposure [Nelson 2014].

These risks are best addressed through professional and patient education about proper prescribing and safe use, and on improving methods of monitoring. Several such measures are in place for TIRF products, starting with the TIRF REMS Access Program. REMS guidelines have also been included in the 2016 National Comprehensive Cancer Network guidelines for physicians who treat patients with cancer-related pain [NCCN 2016]. In addition, some TIRF products incorporate physical prevention in the form of child safety kits to further reduce the risk of accidental exposure in children [Lovegrove 2015].

1.4. History of the TIRF REMS Access Program

The TIRF REMS Access Program is an ongoing collaborative process with FDA, with continual review and updating in consideration of FDA requirements and recommendations. TIRF products are associated with significant risks, and the REMS program is intended to help prescribers and patients use these products safely.

Before the TIRF REMS Access Program, TIRF products were approved for the treatment of BTCP with individual risk reduction plans, either risk mitigation programs (Actiq®, Fentora®), or product-specific REMS (Abstral®, Lazanda®, Onsolis®, Subsys®). It soon became apparent that compliance with these individual programs would become burdensome to the healthcare community, and so, with FDA guidance and approval, TIRF manufacturers agreed to develop a single, shared REMS program, which was approved at the end of 2011 and launched in the beginning of 2012. Under this new class TIRF-wide REMS, prescribers, pharmacies, distributors, and patients need to enroll in only a single REMS program to prescribe, dispense, or receive TIRF medicines in the outpatient setting.

The TIRF REMS Access Program submits comprehensive annual assessment reports to FDA that evaluate whether the REMS is meeting its goals, and it continues to evolve with the changing environment and expectations regarding opioid use and safety. In 2012, a non-compliance protocol was established to monitor for and address prescriber, pharmacy, and distributor activities that are not in accordance with the TIRF REMS requirements. The non-compliance program has been enhanced to include monitoring of closed system pharmacy

dispensing and inpatient pharmacy audits. Enrollment and education materials have been modified to address knowledge gaps identified through Knowledge, Attitudes, and Behaviors (KAB) surveys regularly administered to patients, prescribers, and pharmacists participating in the program. The most recent (2017) modification was completed to align safety messages with the prescribing information (labeling) of TIRF products.

1.5. Elements and Processes of the TIRF REMS Access Program

The shared system REMS includes a Medication Guide; Elements to Assure Safe Use (ETASU) of prescriber and pharmacy certification and dispensing to outpatients with evidence of safe use conditions; an Implementation System; and a Timetable for Submission of Assessments. The latest version of the REMS (8 August 2017) is attached as Appendix A.

All stakeholders subject to the TIRF REMS Access Program, including patients, prescribers, pharmacists, and distributors, must be educated on the requirements of the program and document that they understand and will abide by the ETASU through enrollment in the TIRF REMS Access Program. These requirements result in a controlled distribution network whereby TIRF medicines are made available only through and to stakeholders in the program.

To reduce the risk of inappropriate patient selection and ensure appropriate dosing and administration, TIRF medicines for outpatient use are available only through the TIRF REMS Access Program. However, the program does not have legal authority to enforce appropriate prescribing and patient use, nor does it have the capability or intent to limit physicians' ability to prescribe and practice medicine to ensure optimal patient care.

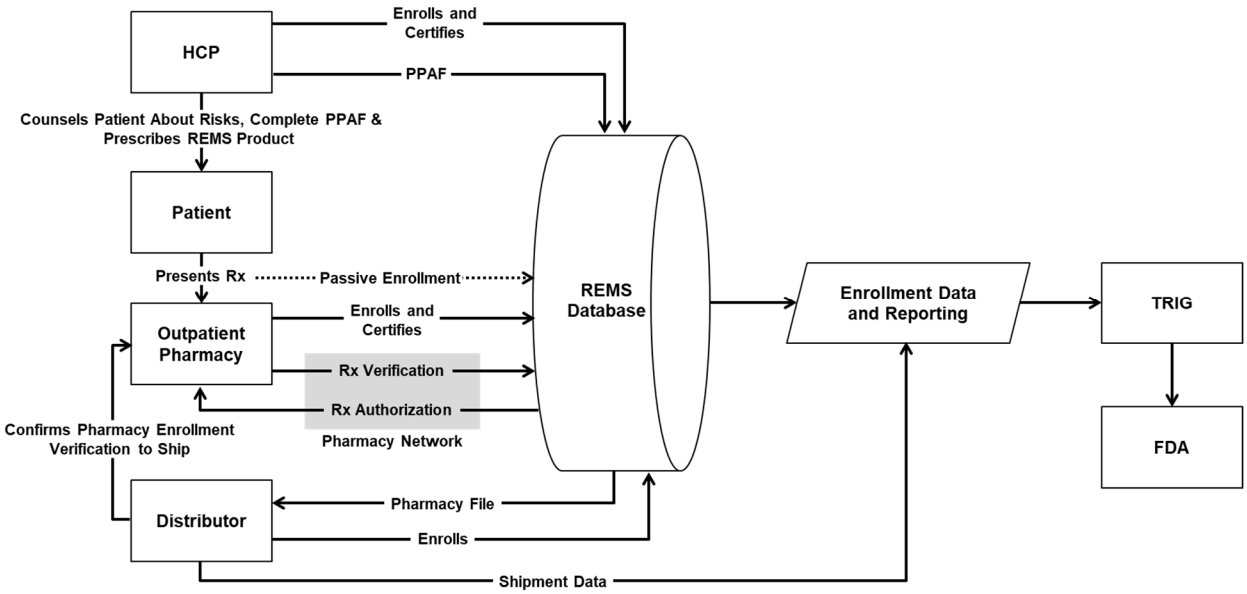
To enroll in the TIRF REMS Access Program, prescribers must review the Education Program, successfully complete the Knowledge Assessment [Appendix B] by scoring 100%, and complete an enrollment form. Prescribers are required to re-enroll in the TIRF REMS program every 2 years.

Both outpatient and inpatient pharmacies that dispense TIRF medicines are required to enroll in the TIRF REMS Access Program. For pharmacies to enroll, a designated authorized pharmacist representative must review the Education Program, successfully complete the Knowledge Assessment, and complete an enrollment form. The authorized pharmacist will then train other pharmacy staff in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access Program, and the pharmacies are audited to ensure that the other pharmacists have been trained. Pharmacies are required to re-enroll in the TIRF REMS program every 2 years.

Patients prescribed TIRF medicines must sign a Patient-Prescriber Agreement Form (PPAF) [Appendix C] with their healthcare provider. With each prescription the dispensing pharmacy provides the patient a Medication Guide containing information regarding the appropriate use of their TIRF. Patients are passively enrolled in the TIRF REMS Access Program when their first prescription is processed by an enrolled pharmacy. A completed PPAF should 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 are allowed within 10 working days from the date that the patient has the first prescription filled, to allow for dose titration if needed. No further prescriptions are dispensed after the 10-working-day window until a completed PPAF is received.

Upon processing of a patient's first TIRF medicine prescription, outpatient pharmacies must verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access Program and that all REMS requirements are met prior to dispensing (Figure 2). For chain and independent pharmacies, verification is done automatically via a pharmacy network provider that links the pharmacy billing claim for any TIRF prescription to the TIRF REMS Access Program database. Closed system outpatient pharmacies are required to verify REMS requirements by phone or fax. Prescription verification is not required for inpatient use of TIRF medicines.

Figure 2: Overview of REMS Processes



1.6. Ongoing Program Assessments

The TRIG collaborates with FDA on an ongoing basis to assess and improve the REMS. Multiple evaluations are conducted within each reporting cycle, and findings from these evaluations are used to identify ways to improve processes and better achieve the goals of the REMS.

1.6.1. Assessment Reporting

The FDA required 6-month and 12-month reports during the first year after approval of the REMS and annually thereafter, with the most recent report (72-month assessment) submitted in February 2018 (Table 2).

Table 2: Schedule of TIRF REMS Access Program Assessment Reports

Assessment Report	Reporting Period	Submission Date
6-Month	28 December 2011 – 27 April 2012	28 June 2012
12-Month	28 April 2012 – 28 October 2012	28 December 2012
24-Month	29 October 2012 – 28 October 2013	28 December 2013
36-Month	29 October 2013 – 28 October 2014	28 December 2014
48-Month	29 October 2014 – 28 October 2015	28 December 2015
60-Month	29 October 2015 – 28 October 2016	28 December 2016
72-Month	29 October 2016 – 28 October 2017	28 February 2018[a]

[a] With FDA agreement, submission date moved to incorporate updates based on FDA feedback.

In addition to the annual assessments, supplemental reports, updates and responses are submitted to address FDA recommendations and queries, and teleconferences are conducted to discuss FDA comments. Individual TRIG sponsors also submit product-specific reports and analyses as requested by FDA.

Assessment data are collected from TIRF REMS Access Program utilization statistics, dispensing activity by enrolled pharmacies, the non-compliance plan, safety surveillance by multiple sources, and annual KAB surveys of patients, prescribers, and pharmacies.

Due to reconciliation of duplicate enrollments, numbers per reporting period cited in the following sections may not total the cumulative enrollment numbers.

1.6.2. Modifications to the TIRF REMS Access Program

Pursuant to FDA requests, the TRIG has modified the program and assessments in the following ways:

- Required system enhancement to modify the patient matching to prevent patients from receiving >3 prescriptions without a PPAF and from receiving >3 prescriptions within the first 10 days without a PPAF
- Revised terminology, processes, and definitions for outpatient pharmacies
- Revised attestations for physicians and patients to address concerns regarding patient access
- Revised Program Overviews and Frequently Asked Questions to improve clarity and content
- Updated REMS materials to reflect the completion of the transition phase for the TIRF REMS Access Program
- Requested that TRIG sponsors provide complete listings of adverse event reports in modified CIOMS II line listing format with root cause analysis if the report provides sufficient information
- Added audit of inpatient pharmacies and closed system pharmacies

- Modified the protocol for non-compliance to capture lower levels of non-compliance

1.6.3. Non-Compliance Monitoring

The TIRF REMS Access Program non-compliance protocol was developed in 2012 to guide the review of reports of suspected non-compliance and the conduct of audits to ensure alignment with REMS program goals. It is overseen by the Non-Compliance Review Team (NCRT), consisting of representatives from each of the TRIG sponsor companies.

The goal of the non-compliance protocol is to identify and investigate activities by REMS stakeholders (prescribers, pharmacies, and distributors) that deviate from program requirements. A confirmed non-compliance event is one in which investigation clearly indicates that a program deviation has occurred and/or that program goals are not being met through stakeholder actions. Non-compliance monitoring is limited to the TIRF REMS Access Program requirements; the program is not monitoring prescriber or pharmacist adherence to state or federal laws and regulations.

Non-compliance information is collected through standard program reports, spontaneous reports identified via the REMS program's Call Center, vendor/sponsor reported events, outreach to relevant stakeholders to validate data/information and solicit further information, and review of the TIRF REMS Access database. The data are tracked in the TIRF REMS Access database.

If a non-compliance event is confirmed, additional investigation is conducted to determine the scope, impact, and root cause. Stakeholders are notified of the investigation via a formal letter from the TIRF REMS Access Program and may also be requested to develop a Corrective Action Plan (CAP). All CAPs are reviewed and approved by the NCRT. Stakeholders who fail to respond to a formal letter and request for a CAP may be deactivated from prescribing or dispensing TIRF products.

The NCRT will determine if the Non-Compliance Protocol should be modified as the program evolves. Any changes to the plan proposed by the NCRT will be voted upon by the TRIG and approved by FDA. The full Non-Compliance Protocol is included in Appendix D. The tracked changes in the document show proposed updates based on correspondence with FDA.

1.6.4. Safety Surveillance Data

As of the 36-Month Assessment Report, safety surveillance data are presented from two composite sources: spontaneous reports of AEs of interest (addiction, overdose, death, and pediatric exposure) collected by the individual TRIG sponsors and presented as aggregate data; and findings from the RADARS System, including data derived from the Poison Center Program, the Treatment Center Programs Combined, the Survey of Non-Medical Prescription Drug Use of Prescription Drugs Program, and drug utilization projections provided by IQVIA. In the most recent report, TIRF product results are compared to those of four other opioid products: immediate-release (IR) oxycodone, extended-release (ER) oxycodone, IR hydromorphone, and IR oxymorphone.

1.6.5. Annual Surveys of Patients, Prescribers, and Pharmacies

Samples of prescribers, pharmacists, and patients enrolled in the TIRF REMS Access Program receive annual KAB surveys designed to assess their level of understanding regarding the

appropriate use of TIRF medicines and program requirements. These results are then considered for continuous improvement initiatives.

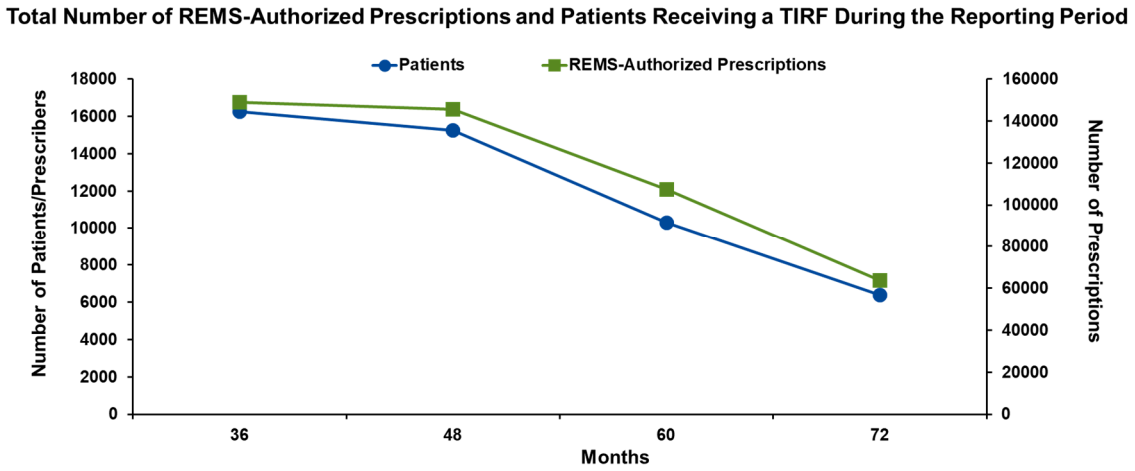
1.7. Program Assessment Results

The following summarizes TIRF REMS Access Program assessment findings first in terms of general program metrics and then by metrics supporting specific program goals. A more detailed presentation of assessment data is found in Section 2.

1.7.1. Program Enrollment

From the inception of the TIRF REMS Access Program in 2012 through the latest assessment report, there has been a significant decrease in the number of active patients and number of TIRF prescriptions authorized. These trends likely reflect changes in medical practice regarding the prescription of opioids; they may also indicate an impact of the REMS program. As shown in Figure 3, compared with the 36-month report, the number of unique patients receiving TIRF prescriptions in the 72-month reporting period has decreased by 61%, and the respective number of prescriptions dispensed has decreased by 57%.

Figure 3: Total Number of REMS Authorized Prescriptions and Patients Receiving a TIRF Medicine During the Reporting Period



Note: A patient is defined as any patient who received one or more prescriptions during the reporting period. The number of prescriptions is defined as the number of prescriptions the REMS authorized for dispensing.
Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

1.7.1.1. Patient Enrollment

As of the end of the 72-month reporting period, 44,724 patients have enrolled cumulatively since program inception. Of these, 2,570 were newly enrolled during this latest reporting period. A total of 6,371 patients received a TIRF medicine during the most recent reporting period. Because patients are passively enrolled with their first prescription, they are not required to re-enroll. Instead, prescribers must renew a patient's PPAF every 2 years. By the design of the program, a patient's enrollment status will never change to inactivated.

1.7.1.2. Prescriber Enrollment

Cumulatively, 17,447 prescribers have been enrolled since the program's inception. At the end of the 72-month reporting period, 6,606 prescribers were enrolled, with 894 newly enrolled during this latest reporting period. Since the inception of the program, 15,605 prescribers have become inactive at some point. As of the end of the most recent reporting period, 10,844 prescribers remained inactive. An outreach to prescribers who inactivated during the 60-month reporting period to ascertain details on why they did not re-enroll showed that the majority no longer had patients for whom TIRF medicines were appropriate.

1.7.1.3. Pharmacy Enrollment

Cumulatively, 50,071 pharmacies have been enrolled since the program's inception. At the end of the 72-month reporting period, 42,615 pharmacies were enrolled, including 717 newly enrolled during this latest reporting period. Since the inception of the program 25,005 pharmacies have become inactive at some point. As of the end of the most recent reporting period, 7,446 pharmacies remained inactive. An outreach to pharmacies who inactivated during the 60-month reporting period to ascertain details on why they did not re-enroll showed that the majority no longer had a need to dispense TIRF medicines.

1.7.1.4. Distributor Enrollment

Cumulatively, 49 distributors have been enrolled since the program's inception. At the end of the 72-month reporting period, there were 32 enrolled distributors, of which two were newly enrolled during this latest reporting period. Since the inception of the program 27 distributors have become inactive at some point. As of the end of the most recent reporting period, 17 distributors remained inactive.

1.7.2. Dispensing Activity

As seen in Figure 3**,** the number of TIRF prescriptions has declined since 2014. During the 72-month reporting period, 69,211 unique prescriptions were submitted for authorization to the TIRF REMS Access Program. Of the total prescriptions, 62,588 (90.4%) were approved for dispensing without encountering any REMS-related rejections. A total of 1,126 (1.6%) prescriptions encountered at least 1 REMS-related rejection before being authorized at outpatient pharmacies. The average time for resolution of rejection reasons after initial REMS rejection was 6.9 days. An additional 5,497 prescriptions encountered at least one REMS-related rejection and were never authorized for dispensing.

1.7.3. Non-Compliance

The number of unique confirmed non-compliance events has been decreasing steadily over the last 4 years: 172 in the 36-month TIRF REMS Access Program assessment, 113 in the 48-month report, 62 in the 60-month report, and 42 in the 72-month report. The majority (72%) of these cases involved prescribers; pharmacies were responsible for 27% of the events and wholesalers 1%. Over the course of the program, 11 prescribers have been permanently deactivated from prescribing TIRF medications due to non-compliance with REMS requirements.

During the 72-month reporting period, there were 29 unique confirmed prescriber events, and 11 non-closed system pharmacy events. All were investigated and the causes determined, with remediation as appropriate.

Audits of 6 closed system pharmacies were conducted during the 72-month reporting period. Three closed system entities were found to be non-compliant with the TIRF REMS Access Program requirements. These pharmacies were re-educated and issued a Notice of Non-Compliance by the NCRT; all non-compliance cases have since been closed.

Audits of five inpatient pharmacies were conducted during this reporting period and no inpatient pharmacy was identified as non-compliant.

1.7.4. Results Related Specifically to Program Goals

1.7.4.1. Overall Program Goal: Mitigating Risks

The overarching goal of the TIRF REMS Access Program is: "to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors…"

RADARS Surveillance Data

The most recent (23 April 2018) RADARS report tracks multiple relevant metrics from four different sources over time, comparing findings from the post-TIRF REMS implementation period (3Q2012 through 2Q2017) to the pre-REMS implementation period (3Q2010 through 2Q2012). TIRF product results are compared to those of four other opioids: IR oxycodone, ER oxycodone, IR hydromorphone, and IR oxymorphone. Prescription data are obtained from IQVIA. Data for major events and deaths (indicative of overdose and death), hospitalizations and emergency department (ED) visits, and pediatric and other exposures are based on spontaneous reporting to the Poison Center Program. Data for past month abuse (indicative of addiction) are reported by the Treatment Centers Combined Program.

The overall incidence of events across the entire 7-year surveillance period (pre- and post-REMS implementation) was very low. In the Poison Center Program, there was an average of <1 exposure involving a TIRF product per quarter for the following outcomes: intentional abuse (total n=24), intentional misuse (total n=18), unintentional pediatric exposure (total n=18), major medical outcome or death (total n=21), and unintentional general exposures (total n=18). There were <2 unintentional therapeutic error exposures per quarter (total n=35), and <4 exposures that resulted in ED visits/hospitalizations per quarter (total n=102). These event numbers were all lower than those for IR oxycodone, ER oxycodone, and IR hydromorphone and similar to those for ER hydromorphone (Table 3).

Table 3: Total Events from 3Q2010 to 2Q2017 in the RADARS Report

Exposure/Events	Drug				
	TIRF Products	IR Oxycodone	ER Oxycodone	IR Hydromorphone	ER Hydromorphone
Intentional abuse	24	5824	2042	879	47
Intentional misuse	18	6883	1181	775	19
Unintentional therapeutic error	35	11571	3519	1777	55
Unintentional general	18	5930	904	428	16
Pediatric unintentional	18	6475	896	442	16
Emergency room visits/hospitalizations	102	38529	8183	4746	126
Major medical outcomes and death	21	3463	1004	530	14
Past month abuse	1418	13996	13604	10109	4599

ER=extended release; IR=immediate release.

The following findings are based on comparison of event rates in the post-REMS implementation period with those in the pre-REMS implementation period and calculated on a per-population and a per-prescription basis.

There was a 43.6% decrease in the average number of prescriptions dispensed per quarter in the post TIRF REMS implementation period relative to the pre TIRF REMS implementation period. Prescriptions dispensed for TIRF products were 79.0% lower in the last quarter of the analysis period (2Q2017) relative to first quarter of the analysis period (3Q2010).

Although the absolute numbers of events were small and have remained relatively consistent, the rates of intentional abuse exposures and exposures resulting in major medical outcomes and death involving TIRF products increased per population in the post-REMS implementation period compared with the pre-REMS period due to the decreasing number of prescriptions. These increases were greater than the changes observed for IR oxycodone, IR hydromorphone, IR oxymorphone, and ER oxycodone.

Population rates of intentional misuse, unintentional therapeutic error, unintentional general exposures, pediatric unintentional exposures, and exposures that resulted in ED visits or hospitalization that involved TIRF products decreased following implementation of the TIRF REMS. Declines in the rates of general unintentional and pediatric unintentional exposures involving TIRF products were greater than those observed with IR oxycodone, IR hydromorphone, IR oxymorphone, and ER oxycodone. Declines in the rates of unintentional therapeutic error and of exposures resulting in ED visits or hospitalizations were greater than

those observed for IR oxycodone and IR hydromorphone and less than those observed for ER oxycodone and IR oxymorphone.

When assessed on the basis of events per prescriptions dispensed, the rates of intentional abuse, intentional misuse, unintentional therapeutic error, and major medical outcomes and death involving TIRF products increased in the post-REMS implementation period, and these increases were greater than those of the comparator opioids. However, as noted above the actual numbers of these types of events remain very low.

The per prescription rates of general unintentional, pediatric unintentional, and ED or hospitalization exposures involving TIRF products decreased in the post-REMS implementation period. For general unintentional and pediatric unintentional exposures, the decreases were greater for TIRF products than those for IR oxycodone, IR hydromorphone, and ER oxycodone and similar to IR oxymorphone. Rates of declines in ER visits or hospitalizations were greater for TIRF products than for IR oxycodone and IR hydromorphone and less than those for ER oxycodone and IR oxymorphone.

In the Treatment Center Programs Combined, declines in past month abuse of TIRF products per population after implementation of the REMS were greater than those observed with IR oxycodone and IR hydromorphone, similar to IR oxymorphone, and less than ER oxycodone. On a per prescription basis, there was a slight increase in the rate of past month abuse post-REMS implementation with TIRF products, which was similar to those of the 4 comparator opioids.

The authors of the RADARS report write that, "The change in rates after the implementation of the TIRF REMS should be interpreted within the context of the rarity of exposures involving TIRF products…. The impact of false positive misclassification on rate estimation is greater for rare events." They conclude that, assuming equal sensitivity and specificity across products surveyed, "abuse estimates for low volume … drugs may be inflated relative to other products."

Spontaneous AEs Reported to the TRIG Sponsors

Spontaneous AE reports submitted to the TRIG sponsors are presented in the aggregate.

The reporting period for the most recent analysis was 29 August 2016 to 28 August 2017. There were 568 unique case reports that met specified criteria for the 4 categories of AEs of interest: death, addiction, overdose, and pediatric exposure.

As expected in a treatment population that includes a large proportion of cancer patients, the great majority of spontaneous AE reports are fatalities. Of the 549 reports of death received in the most recent reporting period, hospice care was noted in >130 cases. Many of these reports lack information about cause of death or indication for TIRF use. Most do not specify what additional opioids or other medications the patient was taking. Some of the reports reference fentanyl but do not include information on the specific formulation, so the TRIG is unable to confirm that the case is in reference to a TIRF product versus a product covered under a different REMS (e.g., fentanyl patch) or illicit fentanyl.

Of the 549 reports of death, 355 cases did not include enough information to allow for an assessment of potential causality. A total of 187 death cases were determined to be not related to the TIRF medication.

Five of the reported deaths had a causality possibly related to the TIRF product. Two additional reports of deaths were determined to be related to the TIRF medication, in which the prescribing physician confirmed inappropriate use in the case narrative.

Of the 24 cases that had more than 1 AE of interest, 1 was categorized as addiction, overdose, and death. The remaining 23 cases are cases of overdose and death. Twenty-one of the 23 cases of overdose and death were from a single consumer source that reported deaths of suspected overdose.

The total number of deaths in the 72-month report increased notably compared to the previous annual report. This increase parallels the overall upsurge of fentanyl deaths reported nationally. It is difficult to distinguish TIRF products from illicit fentanyl postmortem [Warner 2016], and, as noted above, some case reports reference fentanyl but do not include information on the specific formulation, so it is not possible to confirm that a TIRF product was administered. The increase in reported deaths may have been influenced by the recent focus on the opioid epidemic in the US, which could have stimulated greater spontaneous reporting. Spontaneous reporting rates may also be affected by proactive outreach made to patients, caregivers, and prescribers related to TIRF REMS requirements and patient assistance services.

One case of an AE associated with pediatric exposure was reported in the 72-month assessment, and a total of 13, including 1 death, have been reported in the last 4 annual reports combined. Pediatric exposures identified from the RADARS system are discussed above and in more detail in Section 2.4.1.

1.7.4.2. Sub-Goal 1: Ensuring Appropriate Use

The overall REMS goals are to be achieved through 4 sub-goals, the first of which is: "Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients."

Review of the spontaneously reported AE forms and narratives collected by the TRIG sponsors shows that, throughout the course of the TIRF REMS Access Program, there has been no reported case of an AE associated with TIRF use by a non-opioid-tolerant patient. Instances of a spontaneous report of use of a TIRF in opioid non-tolerant patient that are reported to the program are also collected in non-compliance data. To date there have been no such occurrences.

An initial IQVIA study conducted by the TRIG in agreement with FDA found that 42% of the patients receiving TIRF medications between 12 March 2012 and 28 October 2015 were opioid non-tolerant. A subsequent study using IQVIA data, conducted by a single Sponsor, found lower rates of opioid-non-tolerance among TIRF patients in the same timeframe. However, there were differences in the methodology. The TRIG is continuing to evaluate if there have been changes since 2015 and to validate the algorithm to identify opioid tolerance.

1.7.4.3. Sub-Goal 2: Preventing Inappropriate Conversion

The second sub-goal of the program is: "Preventing inappropriate conversions between TIRF medicines."

As noted in the REMS, when switching from one TIRF medicine to another, dosing should not be matched on a microgram-per-microgram basis but should start with the lowest dose of the new TIRF, except in a few specific instances as indicated in product labeling. Review of the

forms and narratives for spontaneously reported AEs of interest collected by the TRIG sponsors shows no case of a reported AE associated with inappropriate conversion over the life of the REMS program.

In collaboration with FDA, the TRIG has conducted a persistency analysis of 18,160 patients in the REMS program's pharmacy network database to determine the risk of inappropriate conversion. This analysis found that 19% of these patients were switched from 1 TIRF product to another. The analysis did not have the level of detail to determine the doses switched.

1.7.4.4. Sub-Goal 3: Preventing Accidental Exposure

The third sub-goal is: "Preventing accidental exposure to children and others for whom it is not prescribed."

Spontaneous AE reports collected by the TRIG sponsors show 1 case of pediatric exposure in the most recent (72-month) assessment, and 13 cases overall during the last 4 annual reports. The most recent RADARS report supports these findings, showing extremely low numbers of children accidentally exposed to TIRF medicines (20 in all since 2010) compared with more frequently used opioids. While changes in rates must be interpreted with caution when events are relatively rare, the RADARS data also show that the rate of childhood exposure to TIRF products per 100,000 patients has declined from the pre-REMS to the post-REMS period.

1.7.4.5. Sub-Goal 4: Educating Stakeholders

The fourth sub-goal is: "Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines."

Ongoing education of all stakeholders is a hallmark of the REMS TIRF Access Program, with evidence supporting success in this regard. Education starts with the mandated prescriber Knowledge Assessment as part of the enrollment process and the Medication Guides, PPAF, and Patient Overview for patients. The program conducts audits of pharmacies to ensure the dissemination of information regarding REMS requirements. Results of the periodic KAB surveys show a high level of understanding about the risks of abuse, addiction, and overdose among patients, prescribers, and pharmacies that has been maintained or improved over time.

The latest (72-month) assessment report found that patients had an average knowledge score of 86% for 5 of the 6 key risk messages in the survey. Prescribers had an average knowledge score of 87% for all risk messages. Of the 38 key message questions or items included in the survey, prescribers had a correct response rate of >80% (the threshold agreed upon with FDA) on 31 items. Pharmacists had a correct response rate of >80% on 23 of 36 items.

The KAB surveys have also identified specific areas for educational improvement: understanding the need to stop TIRF medications when around-the-clock opioids are stopped (patients, prescribers, and pharmacies); understanding the definition of opioid tolerance (prescribers); and understanding the indications for TIRF medications (patients and pharmacies). Working with FDA, the TRIG is addressing or planning to address these educational gaps, as discussed in Section 5 (Proposed REMS Program Changes) and Section 6 (New and Updated Assessments).

1.7.5. Conclusions from the Assessment Results

The key findings from the TIRF REMS Access Program evaluations are:

- The total number of patients receiving TIRF medications and TIRF medication prescriptions has declined since the initiation of the program, and this trend continues in the most recent reporting cycle
- TIRF prescriptions are subject to a safety adjudication by the TIRF REMS Access Program, which helps ensure that REMS requirements are met
- The non-compliance program effectively identifies and investigates stakeholders who do not follow REMS procedures. The rate of confirmed non-compliance events has decreased over the past four annual reports, indicating that prescribers and pharmacies are compliant with REMS requirements. Over the course of the program, 11 prescribers have been permanently deactivated from prescribing TIRF medicines
- According to RADARS surveillance data, the number of AEs of interest, including overdose, death, and pediatric exposure, is very low, averaging <1 per quarter since 2010
- Aggregate spontaneous reporting of AEs collected by the TRIG confirms that accidental exposure in children is extremely rare
- Spontaneously reported AEs do not show evidence of inappropriate conversion between TIRF products. A persistency analysis found that 19% of patients switched from 1 TIRF regimen to another and were therefore potentially at risk of inappropriate conversion
- Results from KAB surveys for all stakeholders show a high level of understanding of most key risk messages that has been sustained or increased over time.

Based on these assessment data, the TIRF REMS Access Program is meeting its goals as designed and implemented. At the same time, these assessments and other ongoing reviews indicate room for continued improvement in specific areas of education and safety monitoring.

1.8. Assessment Gaps and Limitations

Post-marketing safety surveillance based on AEs spontaneously reported to pharmaceutical manufacturers has several limitations, including possible multiplicity (a single event may be reported by several different sources); frequently unknown or misattributed cause of death, especially among patients at or near end of life; and frequent inaccuracy in terms of concomitant medications, both prescribed and illicit. For the TIRF products, some spontaneously reported cases refer to fentanyl but do not include information on the formulation, so that involvement of a TIRF medication cannot be confirmed.

Currently, spontaneous AE reporting is the primary source of REMS assessment data for capturing inappropriate use such as TIRF prescriptions given to non-opioid-tolerant patients or inappropriate conversion from one TIRF medication to another. These incidents do not, however, necessarily lead to AEs that would be captured by spontaneous reporting, nor would they be clearly evident in the event narratives. Additional types of studies are needed (and are being

implemented or considered by the TRIG sponsors) to provide better monitoring of TIRF use in non-opioid-tolerant patients and of inappropriate conversions.

The RADARS report also relies on spontaneous reporting to the Poison Center Program for its data on intentional and unintentional exposure, pediatric exposure, emergency department visits and hospitalizations, and major medical outcomes and death. As the RADARS authors note, patients and family members do not always call a poison center to report an event. Thus, the number of events in this analysis may be underestimated, although usually representative of trends over time.

However, the very low numbers of reported events with TIRF products pose a different problem. These numbers are so low that the pre- and post-REMS trends, compared with other, more-widely used opioids with greater numbers of reported events, may be of limited utility. This point is made by the RADARS authors, who note a greater possibility of false positive findings in the trends analyses when the absolute numbers are so low.

The KAB surveys of patients, prescribers, and pharmacies enrolled in the TIRF REMS Access Program show generally high levels of understanding of key risk messages, but they also indicate consistent sub-par performance by prescribers and pharmacies on specific questions regarding the definition of opioid tolerance and the proper use of TIRF drugs in the context of maintenance opioid treatment for pain relief. The TIRF sponsors agree that additional education with updated wording to clarify messages is required on these topics and conclude that the surveys themselves require revised text to more precisely identify areas of educational need.

1.9. Proposed REMS Program Changes

Throughout the life of the TIRF REMS Access Program, changes and improvements have been continuously made in collaboration with FDA and in response to the Agency's review and feedback of the annual assessment reports. New proposed TIRF REMS program changes include:

- Working with FDA to update educational materials to reinforce the messages not clearly understood as evidenced by low-scoring KAB questions, such as prescriber understanding of opioid tolerance and prescriber and pharmacist understanding of the need to start TIRF treatment only if around-the-clock opioid therapy is ongoing and to stop TIRF treatment if opioid maintenance is discontinued
- Upon identifying changes to the educational materials, align the Knowledge Assessment to be consistent with the education materials
- Updating the non-compliance protocol in accord with FDA recommendations so that prescribers will be flagged at first occurrence of patient enrollment without a PPAF submitted within 10 days, and streamlining the notification and warning process so that the first non-compliance offense results in a notice, the second in a warning, the third in suspension from the program, and the fourth in permanent deactivation from prescribing TIRF products
- Revising the PPAF to include a prescriber attestation to confirm that the patient is opioid tolerant

- Adding attestation language to all pharmacy enrollment forms to allow the program to further audit pharmacies for REMS compliance
- Increase surveillance of prescriber non-compliance with the goal of reducing the possibility of patients being enrolled without a PPAF

1.10. New and Updated Assessments

In addition to the activities and plans outlined in the preceding section, the TRIG sponsors plan the following assessments to improve the evaluation of the TIRF REMS effectiveness:

- Working with FDA to develop two separate studies (Drug Involved Mortality data and Optum/Humedica) to assess the risk of accidental exposure of TIRF products to children, which would supplement the current spontaneous reporting of pediatric exposure events.
- An IQVIA study was conducted to evaluate the occurrence of prescribing to opioid-tolerant and opioid-non-tolerant patients. TRIG is now working with FDA to validate the study algorithm defining opioid tolerance for broader use in identifying opioid-tolerant patients appropriate for TIRF administration.
- Working with FDA to plan studies that involve detailed review of medical records. These will include analysis of fatal and non-fatal overdose in opioid tolerant versus opioid non-tolerant TIRF users.

1.11. Conclusions

Overall, the TIRF REMS Access Program is generally meeting its goals of ensuring safe and appropriate use of TIRF products, and the TRIG is working constantly within the industry and with FDA to refine the program as needed. A comprehensive array of evidence-based metrics supports the elements and execution of the REMS, and lessons learned from these assessments and FDA reviews are guiding ongoing improvement.

TIRF products offer a means for appropriate patients to receive fentanyl in accessible formulations. These medicines are critically needed by cancer patients, many of them at end of life, whose spontaneous breakthrough cancer pain is so severe and disabling that no other form of pain management provides appropriate relief. TIRF products should be prescribed in the context of around-the-clock opioid therapy, which ensures that the patients are opioid-tolerant and can safely receive appropriate doses of fentanyl.

TIRF products are the only medicines specifically indicated for the treatment of BTCP. BTCP can be severe and debilitating, having an enormous impact on the lives of a substantial number of cancer patients. For these patients, the REMS program enables continued access to urgently needed TIRF medicines within a safe and carefully monitored framework of treatment. Recommendations for further improvements to the program should not negatively affect this access.

The TIRF REMS Access Program was initiated in the context of a growing opioid crisis. In the 6 years since the program began, patient enrollment and prescription volume have declined dramatically. The prescription opioid market has changed as public perception and medical practice have changed.

The TIRF REMS Access Program continues to evolve in response to this changing environment. Progress has been made in educating prescribers, pharmacists, and patients about appropriate use of TIRF medicines. Although RADARS surveillance reporting shows a very low incidence of death, overdose, and pediatric or other inadvertent exposure to TIRF medicines over the life of the REMS program, the TRIG continues to advance its efforts to evaluate and mitigate risk. In collaboration with FDA, the TRIG has generated additional studies to better understand the risk of inappropriate conversion and of overdose in opioid-tolerant and non-tolerant patients. Further knowledge is needed to fully quantitate the risk of pediatric exposure, and the TRIG is evaluating data sources for assessment in this area. Work is also underway toward developing a validated algorithm that will help healthcare professionals define opioid tolerance.

The TIRF REMS Access Program has demonstrated the ability to educate prescribers and pharmacists about the appropriate use of TIRF medicines. The TRIG sponsors will work with FDA to ensure that the program continues to build on the progress made and to address areas of need.

The remainder of this document will focus primarily on a more detailed presentation of the program assessment data.

2. ASSESSMENT RESULTS

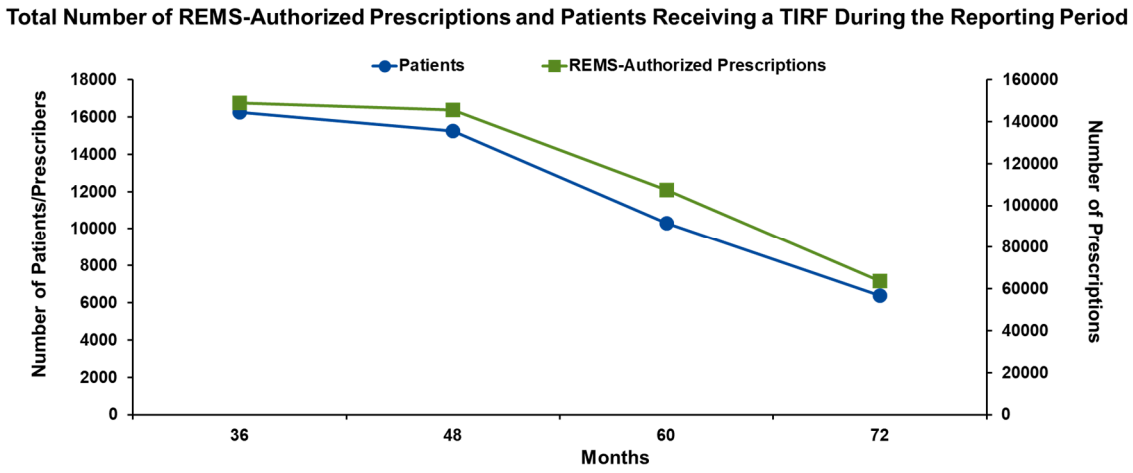
All TIRF REMS Access Program metrics are assessed annually, with data collected from program utilization statistics, dispensing activity for enrolled pharmacies, non-compliance monitoring, safety surveillance data from multiple sources, and periodic KAB surveys of patients, prescribers, and pharmacies. Annual assessment reports are delivered to FDA for review and include recommendations for areas of further development. Since the program was approved by FDA on 28 December 2011 and launched on 12 March 2012, reports have been submitted at 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, and 72 months. The most recent report covers the time period of 29 October 2016 to 28 October 2017 and was submitted 28 February 2018.

2.1. Program Utilization by Stakeholders

The TIRF REMS Access Program enrolls the following stakeholders: patients, prescribers, pharmacists and distributers. Patients are passively enrolled upon their first TIRF prescription and are never inactivated. Prescribers are enrolled upon meeting prescriber-specific education and administrative requirements, must re-enroll in the program every 2 years, and must renew the PPAF with each patient every 2 years. Pharmacists enroll by satisfying the pharmacist-specific education and administrative requirements and must re-enroll every 2 years. Similarly, distributers/wholesalers must meet specific requirements to enroll and must renew every 2 years.

From the inception of the TIRF REMS Access Program in 2012 through the latest (72-month) assessment report, there has been a significant decrease in the number of patients receiving prescriptions and the number of prescriptions that were authorized by the REMS. Months 36 through 72 are shown in Figure 4.

Figure 4: Total Number of REMS Authorized Prescriptions and Patients Receiving a TIRF During the Reporting Period

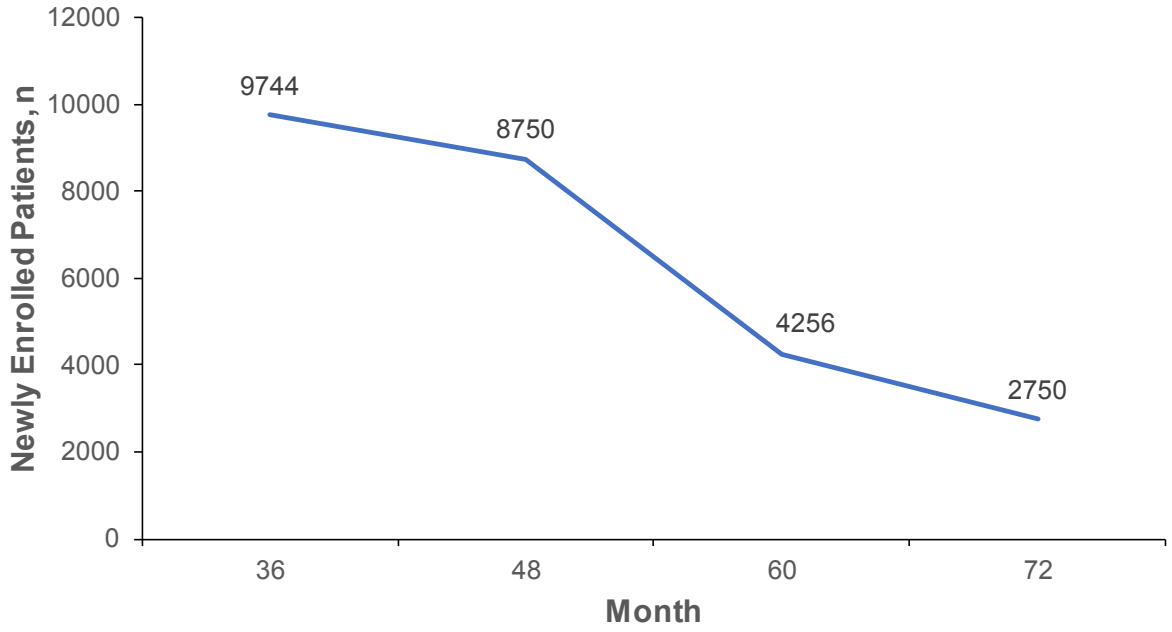


Note: A patient is defined as any patient who received a prescription under the TIRF REMS Access Program during the reporting period. The number of prescriptions is defined as the number of prescriptions the REMS authorized for dispensing.
Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

2.1.1. Patient Enrollment

Based on paid claims data, 6,371 unique patents were dispensed a TIRF drug during the latest (72-month) reporting period (29 October 2016 - 28 October 2017). A total of 2,570 patients were newly enrolled, continuing a declining trend in new patients begun at month 36 (Figure 5). As of the end of this reporting period, 44,724 patients were cumulatively enrolled over the 5 years of the TIRF REMS Access Program (28 December 2011–28 October 2017).

Figure 5: Number of Newly Enrolled Patients as of the End of Each Reporting Period

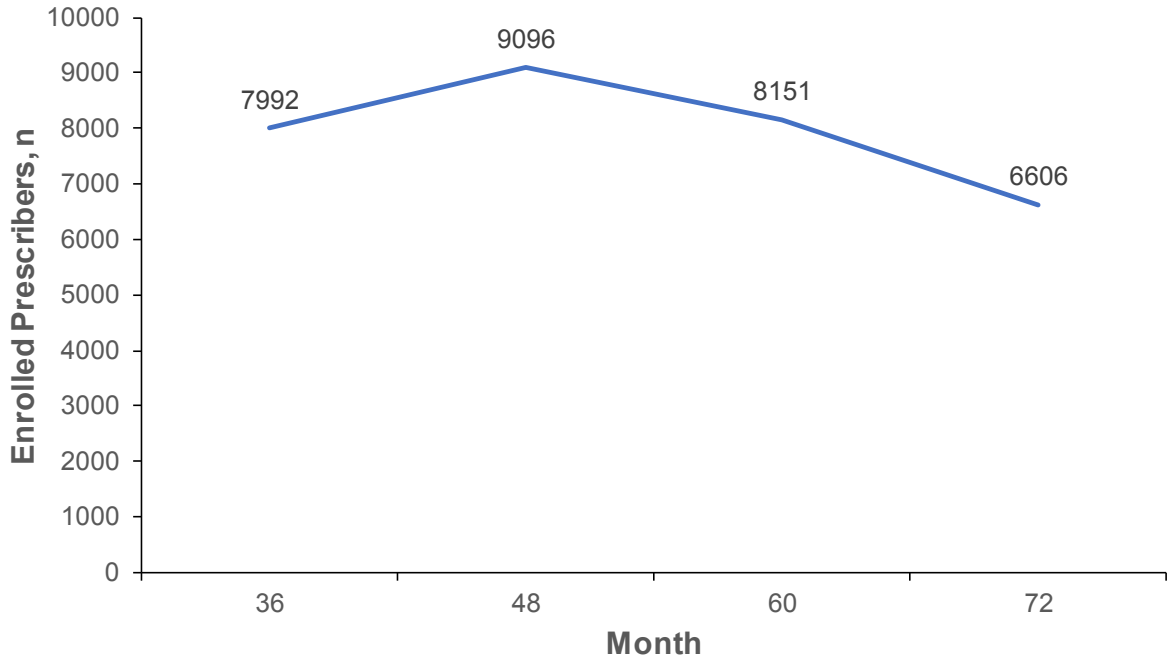


Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

2.1.2. Prescriber Enrollment

Cumulatively, 17,447 prescribers have been enrolled since the program's inception. A total of 6,606 prescribers were actively enrolled during the most recent reporting period, including 894 newly enrolled prescribers, 1,775 re-enrolled prescribers, and 3,937 prescribers remaining enrolled from the previous period. Overall, the results of the 72-month assessment continued a downward trend from month 48 in number of new prescribers, prescribers with enrollment activity in the reporting period, and prescribers enrolled as of the end of the reporting period (Figure 6).

Figure 6: Total Number of Prescribers Enrolled As of the End of Each Reporting Period



Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

During the 72-month reporting period, 3,241 prescribers were inactivated at least once, almost all (3,217 [99.3%]) due to enrollment expiration; by the end of the reporting period, 2,756 (85.7%) of these prescribers continued to have an expired status. At the end of this reporting period, 8,067 prescribers remained inactive from a previous reporting period, for a total of 10,844 inactivated prescribers. Overall, 15,605 prescribers have ever been inactivated during all reporting periods. About 400 fewer prescribers were inactivated in this reporting period than during the previous period (month 60), with a similar percentage due to expiration, but a higher percentage of prescribers (85.7 vs 76.4%) remained inactivated at the 72-month time point.

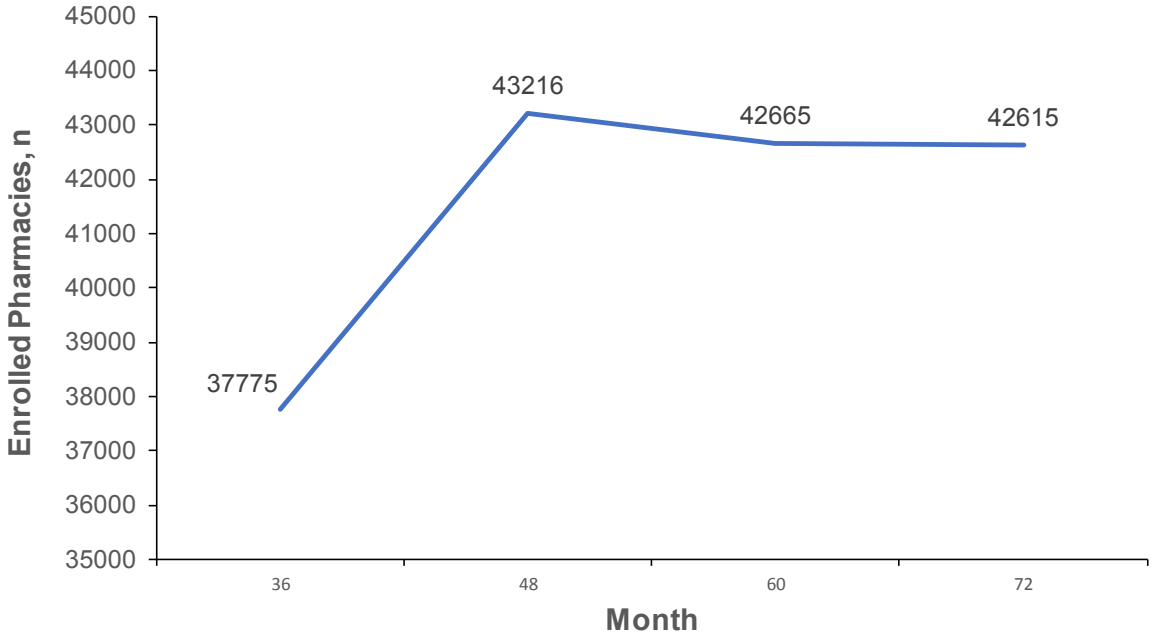
The number of prescribers who attempted enrollment and were still pending for ≥3–6 months or >6 months was 22 and 180, respectively, during the 72-month reporting period. Most of these pending enrollments were due to lacking the prescriber attestation and/or training not completed. Other reason for incomplete enrollment included invalid DEA numbers, failure of knowledge assessments, and prescriber is not authorized to prescribe controlled substances (TIRF medicines).

2.1.3. Pharmacy Enrollment

Cumulatively, 50,071 pharmacies have been enrolled since the program's inception. Of these enrolled pharmacies, 49,602 were non-closed system dispensing pharmacies (1,259 inpatient pharmacies, 41,726 chain pharmacy stores, 6,617 independent outpatient pharmacies) and 367 closed system dispensing pharmacies.

A total of 42,615 pharmacies were enrolled at the end of the 72-month reporting period. This total included 17,580 pharmacies with enrollment activity during this reporting period, comprising 717 (4.1%) newly enrolled and 16,863 (95.9%) re-enrolled pharmacies, and 25,035 active enrollments remaining from a previous reporting period (Figure 7). The percentage of newly enrolled pharmacies of total enrolled pharmacies has declined from month 48 through 72 (20.6%, 5.8%, and 4.1% for month 48, 60, and 72, respectively).

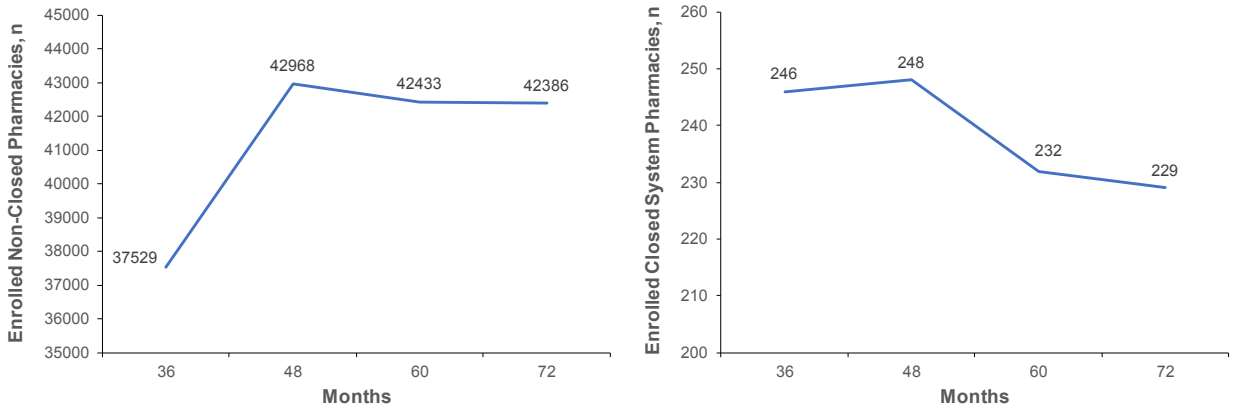
Figure 7: Total Number of Pharmacies as of the End of Each Reporting Period



Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

The total number of non-closed and closed pharmacies are shown in Figure 8; both declined from month 48 to 72.

Figure 8: Total Number of Non-Closed and Closed System Pharmacies Enrolled as of the End of Each Reporting Period



Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

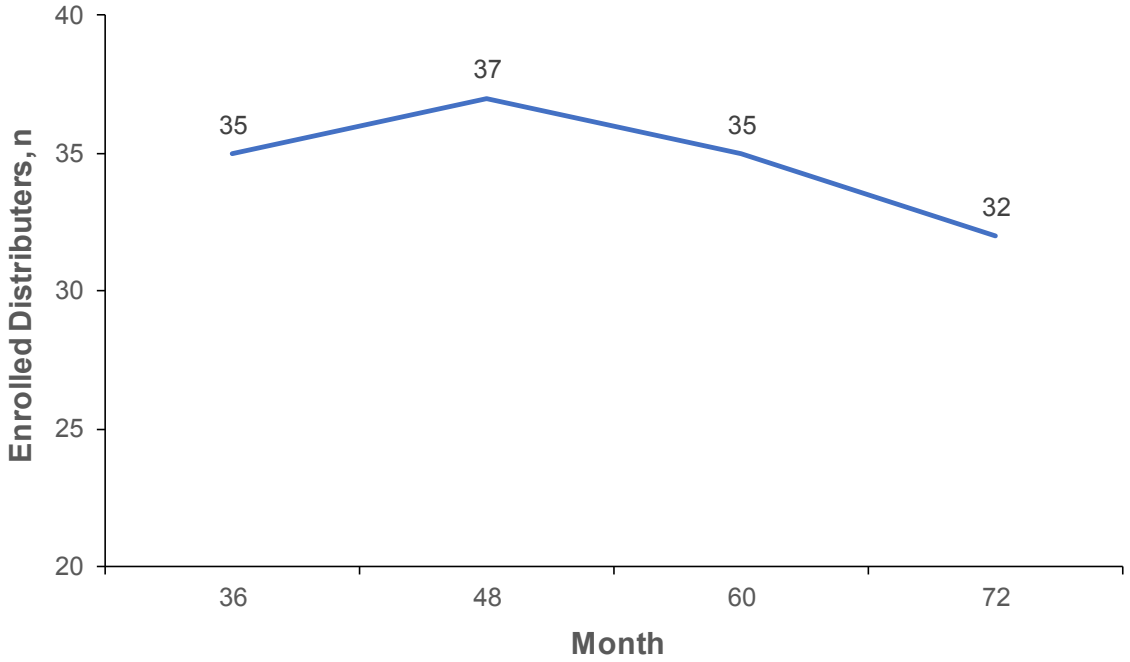
The number of pharmacies with pending enrollments for ≥3–6 months or >6 months was 21 and 111, respectively, during the 72-month reporting period, all from non-closed system pharmacies. The most common reasons cited for ≥3–6 months and >6 months pending enrollments were no attestation (28.8 and 45.0%, respectively), pending test transaction verification (71.4 and 53.2%, respectively), and training not complete (28.6 and 32.4%, respectively).

In the 72-month reporting period, 7,911 pharmacies were inactivated at least once; the most common reason was expired enrollment (7,705 [97.5%]). The number of pharmacies that remained inactive as of the end of the 72-month reporting period was 1,470.

2.1.4. Distributer Enrollment

Of the 14 wholesaler/distributers with enrollment activity during the 72-month reporting period, 2 (14.3%) wholesalers/distributors were newly enrolled and 12 (85.7%) re-enrolled in the TIRF REMS Access Program. Including those enrolled in a previous reporting period (18), the total number of wholesalers/distributors enrolled at the end of the current reporting period was 32 and the cumulative number of wholesalers/distributors ever enrolled was 49; distributer enrollment has declined from month 48 (Figure 9).

Figure 9: Total Number of Distributors Enrolled as of the End of Each Reporting Period



Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

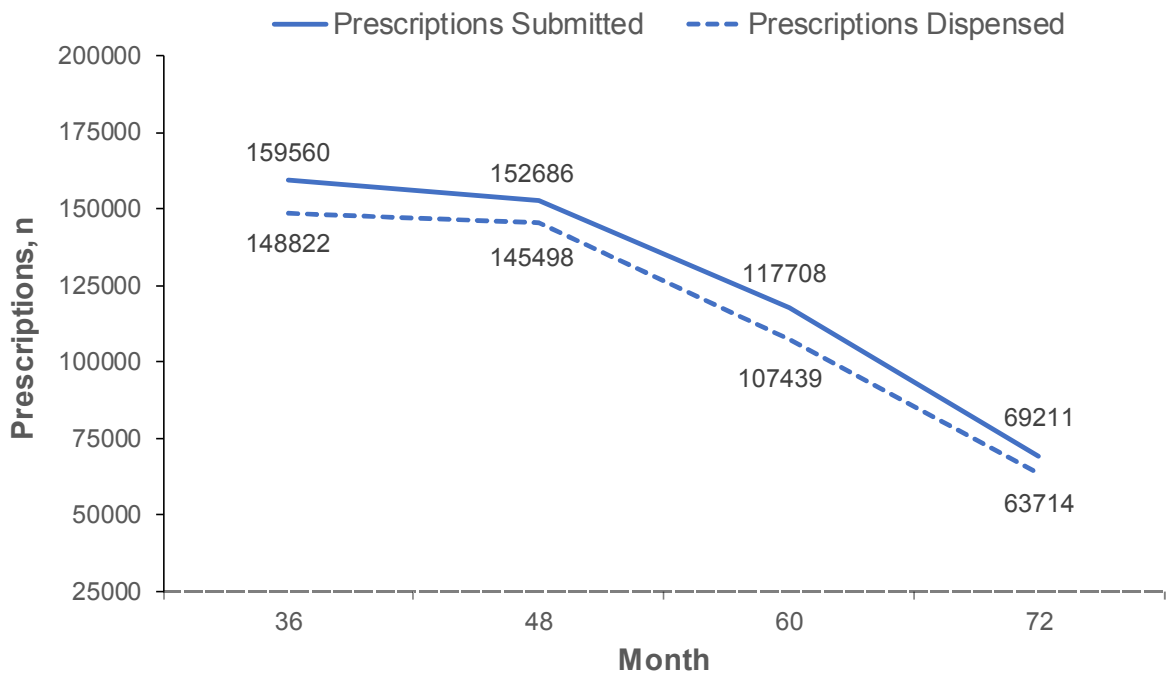
Due to enrollment expiration in the 72-month reporting period, 5 wholesalers/distributors were inactivated and 3 had not re-enrolled, 2 because they no longer dispense TIRF medications and the other due to mistaken enrollment type (pharmacy mistakenly enrolled as distributor).

2.2. Prescription Dispensing

2.2.1. Prescriptions Submitted and Authorized

A total of 69,211 prescriptions were adjudicated for safety by the TIRF REMS Access Program in the 72-month reporting period, and 63,714 were ultimately authorized and dispensed. These numbers have declined steadily over the last 4 reporting periods (Figure 10). Of all prescriptions submitted in the 72-month report, 90.4% (62,588) were approved for dispensing without encountering any REMS-related rejections.

Figure 10: Number of Prescriptions Submitted and REMS-Authorized During Each Reporting Period



Sources: TIRF REMS Access Program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

2.2.2. Prescriptions Encountering REMS-Related Rejections

Of the 69,211 unique prescriptions submitted for approval during the 72-month report period, 1,126 (1.6%) prescriptions encountered at least 1 REMS-related rejection prior to being authorized for dispensing, all from outpatient pharmacies. The most frequent rejection reasons for independent pharmacies (n=672) and chain pharmacies (n=454) were PPAF expired (29.9 and 24.4%, respectively), PPAF incomplete (25.9 and 23.8%), prescriber identification (ID) not registered (14.4 and 9.9%, respectively), zip code missing (10.6 and 10.4%, respectively), and prescriber last name did not match a registered prescriber (5.2 and 25.1%, respectively).

Of all the unique prescriptions submitted for approval, 5,497 (7.9%) prescriptions encountered at least 1 REMS-related rejection in the 72-month reporting period and were never authorized for dispensing. The percentage of these never authorized prescriptions varied from 8.7% at 60 months and 4.7% at 48 months. The most common rejection reasons during the 72-month reporting period for independent pharmacies (n=2,047) and chain pharmacies (n=3,430) were prescriber ID not registered (38.0 and 26.0%, respectively); prescriber terminated (22.6 and 10.7%, respectively); zip code missing (15.1 and 16.7%, respectively); and prescriber last name did not match a registered prescriber (10.5 and 48.0%, respectively). The most frequent rejection reasons for closed system pharmacies (n=20) were prescriber ID not registered (75.0%) and prescriber last name did not match a registered prescriber (15.0%).

2.2.3. Time to Authorization

During the current reporting period, the mean and median time to authorization for the 1,126 prescriptions that received at least 1 REMS-related rejection prior to being authorized for dispensing was 6.9 and 2.0 days, respectively. The mean was 7.8 days (median 2.8 days) for chain pharmacy stores and 6.4 days (median 1.9 days) for independent outpatient pharmacies, with no REMS-related rejections for closed system pharmacy prescriptions. These times were slightly longer than the previous reporting period.

Patients are passively enrolled in the TIRF REMS Access Program through submission of a prescription to a pharmacy for a TIRF medicine. Across all pharmacies in the reporting period, 1,739 prescriptions were dispensed to 1,505 newly enrolled patients within the first 10 days after patient enrollment. Within 10 days of passive enrollment, 533 (35.5%) of these patients received 1 prescription fill and 31 patients received 2 prescription fills without a PPAF on file. No patient without a PPAF on file received 3 or more prescription fills during the initial 10-day period. All 564 of these patients who filled prescriptions within 10 days of enrollment and without a PPAF on file had their prescriptions filled through chain or independent pharmacies. Closed system pharmacies dispensed 3 patients a prescription with the first 10 days, none without a PPAF on file.

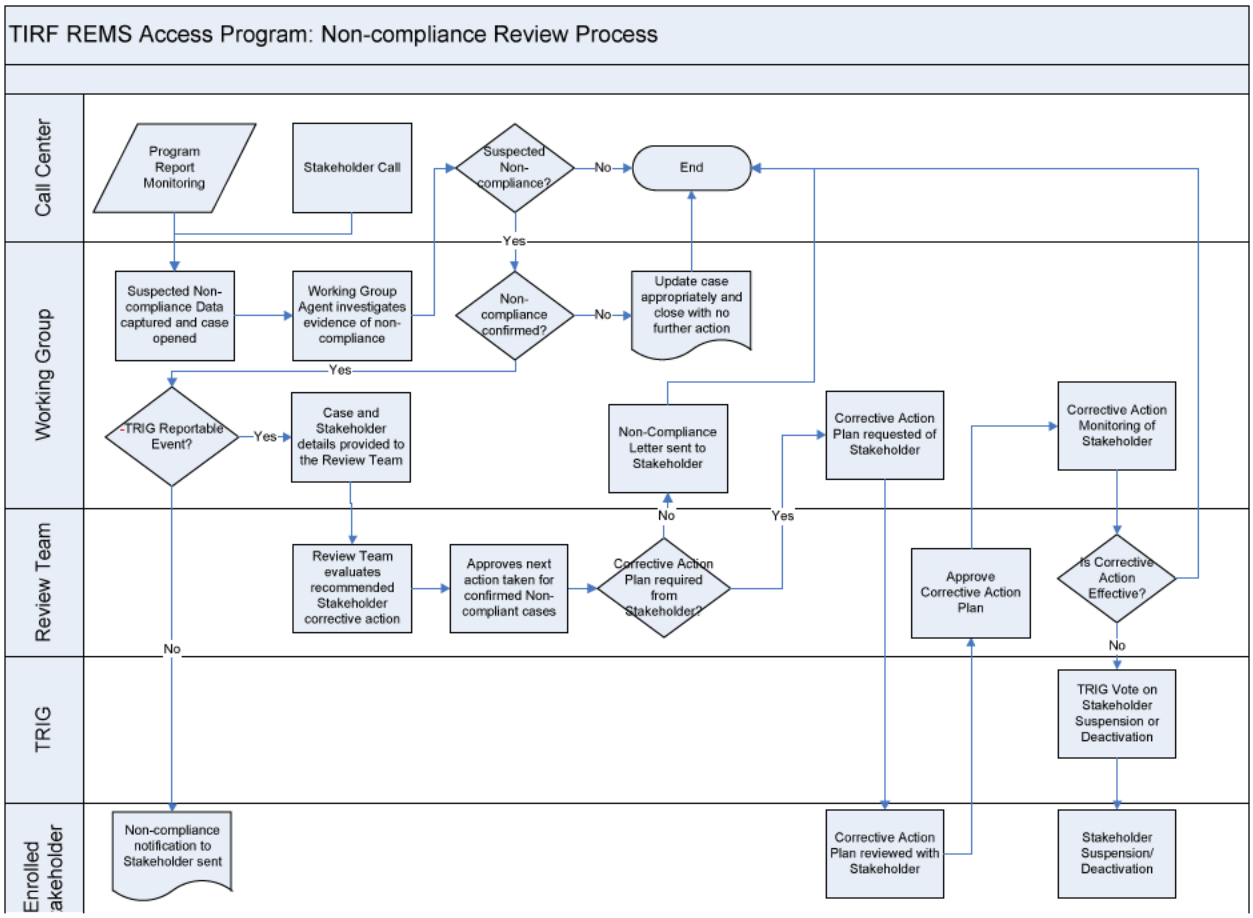
No prescriptions were dispensed beyond 10 days after enrollment without a PPAF in the current reporting period or in the previous reporting period. Cumulatively, 798 prescriptions have been dispensed beyond the first 10 days without a PPAF, almost all within the first few reporting periods of the TIRF REMS Access Program.

2.3. Non-Compliance Reporting

The goal of the TIRF REMS Access Program Non-compliance Protocol is to identify and investigate activities by REMS stakeholders that deviate from program requirements. A confirmed non-compliance event is one in which investigation clearly indicates that a program deviation has occurred and/or that program goals are not being met through stakeholder actions.

Non-compliance information is collected through standard program reports, spontaneous reports identified via the program's Call Center, vendor/sponsor reported events, outreach to relevant stakeholders to validate data/information and solicit further information, and investigation of the TIRF REMS Access database. The data on each event are tracked through a non-compliance case that is opened on the stakeholder record in the TIRF REMS Access database (Figure 11).

Figure 11: TIRF REMS Access Program Non-Compliance Review Process



If a non-compliance event is confirmed, additional investigation is conducted to determine the scope, impact, and root cause of the event. Stakeholders are notified of the investigation via a formal letter from the TIRF REMS Access Program and may also be requested to develop a CAP. All CAPs are reviewed and approved by the NCRT.

Non-compliance cases are reported via 4 methods: stakeholder non-compliance activity reports table, stakeholder non-compliance narratives, closed system pharmacy audits, and inpatient hospital pharmacy audits. Each unique stakeholder non-compliance case is investigated, and non-compliance activity is generally reported 2 ways during a reporting period, either as a confirmed non-compliance activity report or as a narrative description. If single non-compliance cases are reported concerning the same stakeholder and appear for 2 consecutive assessment reports, the stakeholder's third offense will warrant a CAP. Any confirmed non-compliance event that results in a NCRT "Warning" or is a result of any assessment monitoring (includes closed system monitoring and inpatient-pharmacy audits) is reported in a narrative.

2.3.1. Reported Non-Compliance Activity

The number of unique confirmed non-compliance events has been decreasing steadily over the last 4 years: 141 in the 36-month TIRF REMS Access Program assessment, 106 in the 48-month

report, 58 in the 60-month report, and 40 in the 72-month report. The majority (72%) of these cases involved prescribers; pharmacies were responsible for 27% of the events and wholesalers 1%. Over the course of the program, 11 prescribers have been permanently deactivated from prescribing TIRF medications. As shown in Table 4, the rate of prescriber non-compliance reports per prescriber population and per prescription submitted and dispensed has declined over the last 4 reporting periods.

Table 4: Rates of Prescriber Non-Compliance Reports over Time

Rates[a]	**36-Month Report (N=120 reports)**	**48-Month Report (N=82 reports)**	**60-Month Report (N=50 reports)**	**72-Month Report (N=29 reports)**
Per 1,000 prescribers[b]	15.02	9.01	6.13	4.39
Per 10,000 submitted prescriptions[c]	7.52	5.37	4.25	4.20
Per 10,000 authorized prescriptions[d]	8.06	5.64	4.65	4.55

[a] Rates are based on adjusted data.

[b] The prescriber rates were based on reported number of prescribers enrolled as of the end of the reporting period. The denominators used for the 36-Month, 48-Month, 60-Month, and 72-Month REMS Assessment Report calculations were 7,992; 9,096; 8,151; and 6,606.

[c] The submitted prescription rates were based on the total number of prescriptions submitted for authorization. The denominators used for the 36-Month, 48-Month, 60-Month, and 72-Month REMS Assessment Report calculations were 159,560; 152,686; 117,708; and 69,211.

[d] The authorized prescription rates were based on the number of prescriptions that did not encounter any REMS-related rejections and were dispensed and the prescriptions that encountered at least one REMS-related rejection but were eventually authorized and dispensed.

Note: The denominators used for the 36-Month, 48-Month, 60-Month, and 72-Month REMS Assessment Report calculations were 148,822; 145,498; 107,439; and 63,714.

During the 72-month reporting period, there were 29 unique confirmed prescriber events, and 11 non-closed system pharmacy events. All were investigated and the causes determined, with remediation as appropriate.

During the reporting period, there were 2 instances of a TIRF prescription dispensed by a non-closed system pharmacy that was written by non-enrolled prescribers after receiving a rejection from the TIRF REMS Access Program as described below. There were also 2 instances of a prescription dispensed by a non-enrolled pharmacy, and 1 instance of a TIRF prescription that was dispensed because a pharmacy was able to bypass REMS edits.

No case of a TIRF medicine being prescribed to an opioid non-tolerant individual or of inappropriate conversion between TIRF products was reported to the TIRF REMS Access Program.

2.3.2. Closed System Pharmacy Audits

For closed system pharmacy audits, the REMS Assessment Plan includes verification of training for all pharmacists dispensing TIRF products, numbers of prescription authorizations per closed system, and reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access Program.

Of the 6 closed system pharmacies audited during the 72-month monitoring reporting period at various audit-monitoring periods, 3 were found to be non-compliant with the TIRF REMS Access Program requirements. A non-compliance case was opened for each case, and investigation eventually led to a Warning Letter and request for a CAP for each.

2.3.3. Inpatient Hospital Pharmacy Audits

All inpatient hospital pharmacies enrolled in the TIRF REMS Access Program were invited to participate in the audit process. Once an authorized inpatient pharmacist agreed to participate and the pharmacy qualified as a hospital inpatient pharmacy that dispensed TIRF medicines in the reporting period, the pharmacist completed a questionnaire regarding the number of units dispensed, pharmacist education on the TIRF REMS Access Program, and procedures in place to assure compliance with the TIRF REMS program requirements.

Of the 29 enrolled inpatient locations solicited for participation in the audit, 9 did not respond. Of the remaining 20 pharmacy locations that agreed to participate, 15 were either not a hospital inpatient pharmacy facility or had not dispensed TIRF products in the previous 12 months. The remaining 5 pharmacies that were qualified to participate in the audit completed the questionnaire. Based on the responses, all 5 of the audited inpatient hospital pharmacies were found to be compliant with the TIRF REMS Access Program requirements.

2.4. Safety Surveillance

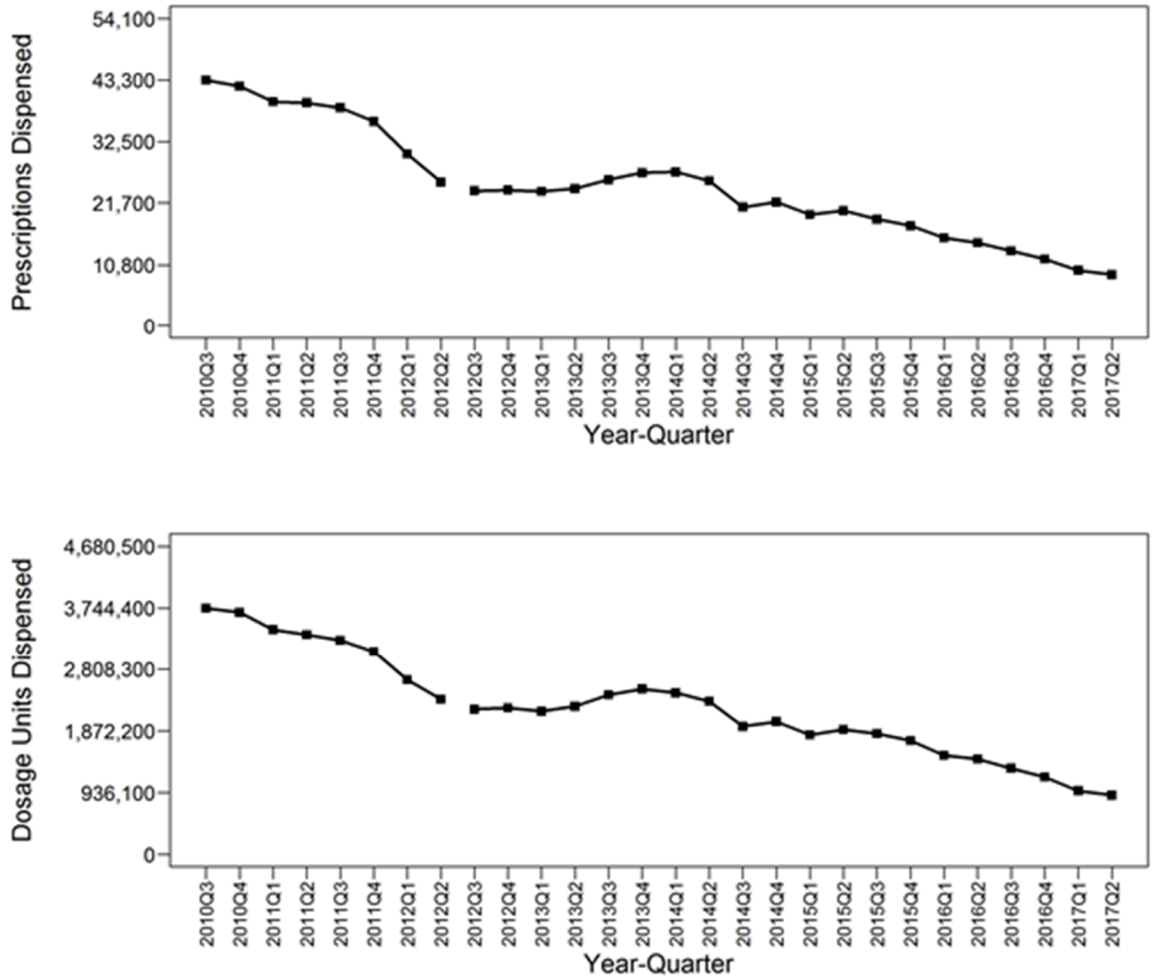
Safety surveillance data are obtained from 2 composite sources: 1) RADARS data derived from the Poison Center Program, the Treatment Center Programs Combined, the Survey of Non-Medical Prescription Drug Use of Prescription Drugs Program, and drug utilization projections provided by IQVIA; and 2) spontaneous reporting of AEs of interest (addiction, overdose, death, and pediatric exposure) collected by the individual TRIG sponsors and presented as aggregate data.

2.4.1. RADARS Surveillance Reporting

The most current (23 April 2018) RADARS report tracks relevant metrics over time from the immediate pre-REMS implementation period (3Q2010-2Q2012) to the post-TIRF REMS implementation period (3Q2012-2Q2017). TIRF product findings are compared with those of 4 other opioids: IR oxycodone, ER oxycodone, IR hydromorphone, and IR oxymorphone. Prescription utilization data reported by IQVIA are projections based on observed retail pharmacy data and population. Data for major medical outcomes (indicative of overdose and death), hospitalizations and ED visits, and pediatric and other exposures are based on spontaneous reporting to the Poison Center Program. Data for past month abuse (indicative of addiction) are reported by the Treatment Centers Combined Program.

Based on IQVIA projections, the average number of prescriptions dispensed per quarter decreased 43.6% in the post TIRF REMS implementation period relative to the pre TIRF REMS implementation period (Figure 12). Prescriptions dispensed for TIRF products were 79.0% lower in the last quarter of the analysis period (2Q2017) relative to first quarter of the analysis period (3Q2010). Corresponding to the number of prescriptions, dosage units also decreased as shown in Figure 12.

Figure 12: TIRF Product Drug Utilization Projections by Quarter (3Q2010-2Q2017)



In the Poison Center Program, an average of <1 exposure per quarter involving a TIRF product was reported for the following outcomes over the entire 7-year surveillance period: intentional abuse (total n=24), intentional misuse (total n=18), unintentional pediatric exposure (total n=18), major medical outcome and death (total n=21), and unintentional general exposures (total n=18). There were <2 unintentional therapeutic error exposures per quarter (total n=35), and <4 exposures that resulted in ED visits/hospitalizations per quarter (total n=102). The number of TIRF-product related events or exposures was much less than those for IR oxycodone, ER oxycodone, and IR hydromorphone, and roughly similar to that for ER hydromorphone (Table 5).

Table 5: Total Events from 3Q2010 to 2Q2017 in the RADARS Report

Exposure/Events	Drug				
	TIRF Products	IR Oxycodone	ER Oxycodone	IR Hydromorphone	ER Hydromorphone
Intentional abuse	24	5824	2042	879	47
Intentional misuse	18	6883	1181	775	19
Unintentional therapeutic error	35	11571	3519	1777	55
Unintentional general	18	5930	904	428	16
Pediatric unintentional	18	6475	896	442	16
Emergency room visits/hospitalizations	102	38529	8183	4746	126
Major medical outcomes and death	21	3463	1004	530	14
Past month abuse	1418	13996	13604	10109	4599

ER=extended release; IR=immediate release.

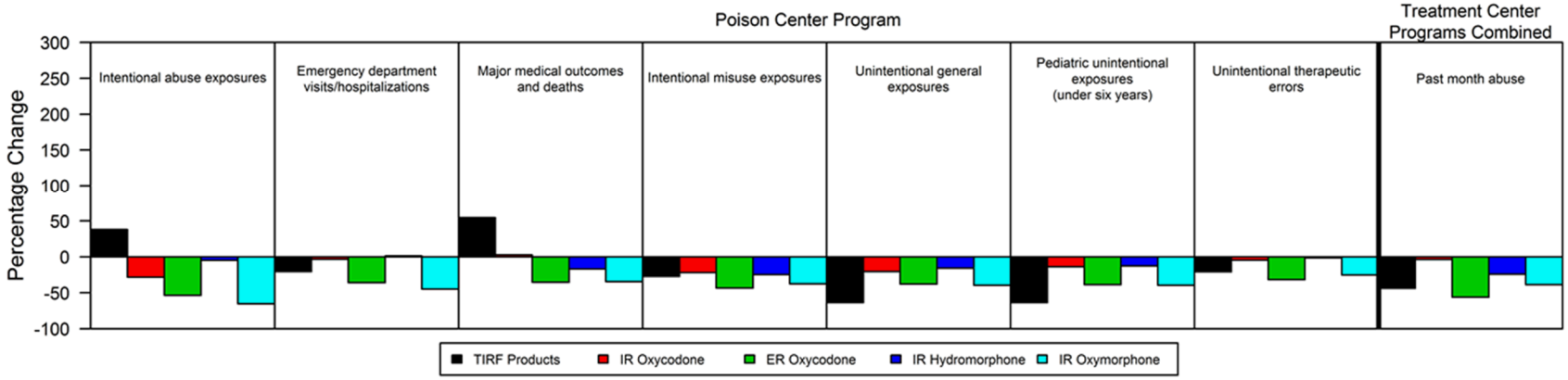
Although the absolute numbers were small, the percentage change in per population rates of intentional abuse and major medical outcomes and death involving TIRF products increased following implementation of the TIRF REMS (Figure 13). These increases were greater than the changes observed for the 4 opioid comparators.

The percentage change by population in rates of intentional misuse, unintentional therapeutic error, unintentional general exposures, pediatric unintentional exposures, and exposures that resulted in ED visits or hospitalization that involved TIRF products decreased following implementation of the TIRF REMS. The decrease in percentage change in rates of unintentional general and pediatric unintentional exposures involving TIRF products following REMS implementation was greater than those observed for the 4 opioid comparators. Unintentional exposures are of particular importance in safety surveillance, for they represent children and adults who accidentally and avoidably received TIRF products, as opposed to those who deliberately sought to misuse TIRF or other opioid drugs.

In the Treatment Center Programs Combined, declines in percentage change in rates of past month abuse of TIRF products per population following implementation of the REMS were greater than those observed with IR oxycodone and IR hydromorphone, similar to IR oxymorphone, and less than ER oxycodone. It should be noted that past month abuse cases frequently include other opioids in addition to TIRF products.

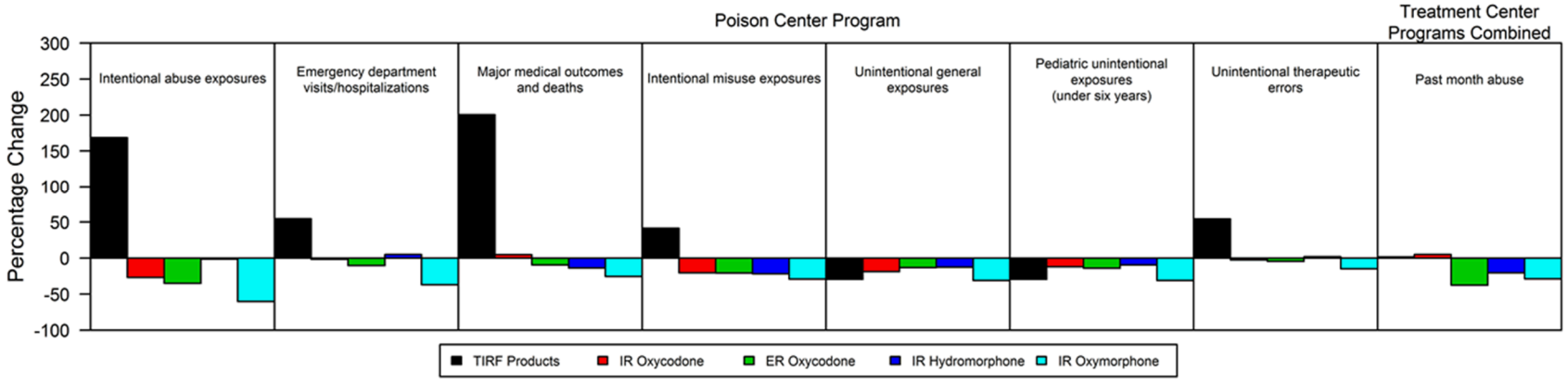
The percentage change in rates per prescriptions dispensed of intentional abuse exposures, ED visits and hospitalizations, exposures resulting in major medical outcomes and deaths, intentional misuse exposures, and unintentional therapeutic errors involving TIRF products increased following implementation of the TIRF REMS (Figure 14). These increases were greater than the changes observed for the 4 opioid comparators.

Figure 13: Percentage Change in Rates Per Population by Drug Group (3Q2010–2Q2017)[a]



[a]A negative percentage change value represents a decrease in the rate in the post-REMS implementation period relative to the pre-REMS implementation period. A positive percentage change values represents an increase.

Figure 14: Percentage Change in Rates Per Prescription by Drug Group (3Q2010–2Q2017)[a]



[a]A negative percentage change value represents a decrease in the rate in the post-REMS implementation period relative to the pre-REMS implementation period. A positive percentage change values represents an increase.

Percentage change in rates of unintentional general exposures and pediatric unintentional exposures by prescriptions dispensed decreased following implementation of the TIRF REMS. These declines were greater than those observed with IR oxycodone, IR hydromorphone, and ER oxycodone, but slightly less than the declines of IR oxymorphone.

In the Treatment Center Programs Combined, the increase of 1.5% in percentage change in rate of past month abuse of TIRF products per population was less than that observed with IR oxycodone; the rates declined for the other comparator products.

The RADARS report found that exposures involving TIRF products are relatively rare. Calculated on a per population basis, the rates of all exposure and event categories assessed in the Poison Center Program in the post REMS implementation period were lower for TIRF products than for IR oxycodone, ER oxycodone, and IR hydromorphone (Figure 15). When calculated on the basis of prescriptions dispensed, exposure rates and events for TIRF medicines were similar to those of the comparator groups in the post-REMS implementation period (Figure 16). In the Treatment Center Programs Combined, the rate of past month abuse with TIRF product per 10,000 prescriptions dispensed in the post-REMS implementation period was higher than those of IR oxycodone, ER oxycodone, and IR hydromorphone.

Figure 15: Outcomes per 100,000 Population with 95% Confidence Intervals by Drug Group in the Post TIRF REMS Period (3Q2012–2Q2017)

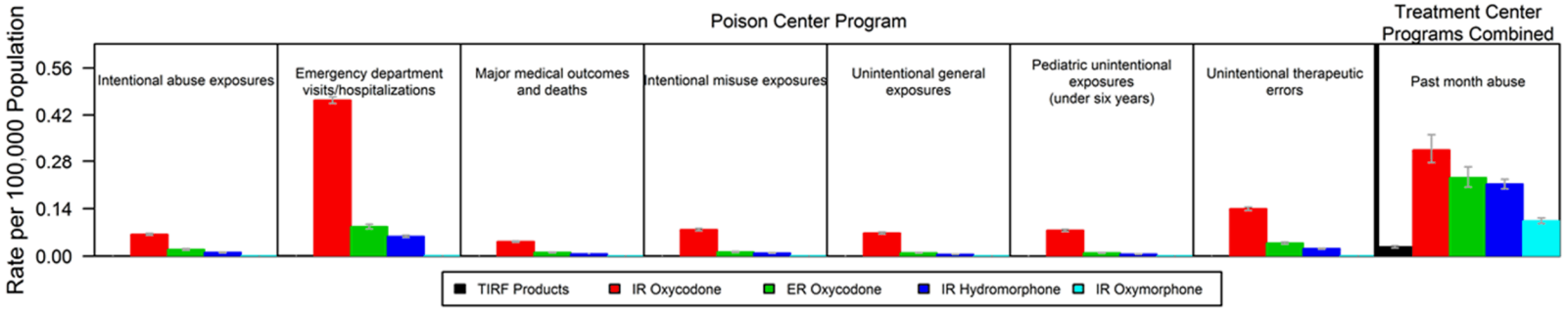
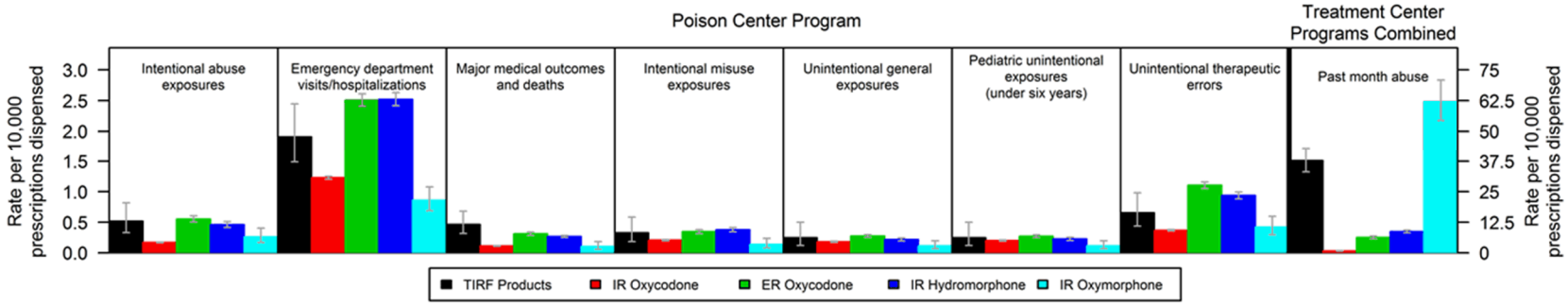


Figure 16: Outcomes per 10,000 Prescriptions Dispensed with 95% Confidence Intervals by Drug Group in the Post TIRF REMS Period (3Q2012–2Q2017)



The authors of the RADARS report write that, "The change in rates after the implementation of the TIRF REMS should be interpreted within the context of the rarity of exposures involving TIRF products…. The impact of false positive misclassification on rate estimation is greater for rare events." Assuming equal sensitivity and specificity across products surveyed, they conclude that abuse estimates for low volume drugs "may be inflated relative to other products."

2.4.2. Aggregate Spontaneous AE Reporting to TRIG Sponsors

As part of the REMS Assessment Plan, the TRIG has used a third party to conduct annual aggregate root cause analyses of all spontaneous AE reports of addiction, death, overdose, and pediatric exposure gathered from the TIRF Sponsors. The most recent (72-month) reporting period used for this analysis was 29 August 2016 to 28 August 2017. A total of 568 unique case reports met the specified criteria for the 4 categories of AEs of interest. Note that cases can have more than 1 AE of special interest. After a review of the 568 MedWatch Forms or narratives, no case was reported of inappropriate conversion between TIRF products. No AE associated with the use of a TIRF product by a patient not tolerant to opioids was discovered in the narratives.

2.4.2.1. Number of Adverse Events of Interest

Of the 568 AEs of interest reported during the current period, 549 (96.7%) had an outcome of death, 10 (1.8%) were reports of addiction, 34 (6.0%) were reports of overdose, and 1 (0.2%) report was for pediatric exposure (Table 6 and Table 7). Whereas reports of addiction and pediatric exposure decreased, reports of deaths and overdoses increased from the previous reporting period.

2.4.2.2. Reporting Rates of AEs of Interest

The reporting rate of each AE of interest was calculated using the number of prescriptions for TIRF products and the number of patients receiving a TIRF product for the reporting interval as denominators. The AE reporting rates per 100,000 prescriptions for each of the AEs of interest by total prescriptions are shown in Table 5 for the 72-month reporting period, along with the adjusted rates for the 60-, 48-, and 36-month reporting periods. In the 72-month assessment, the number of AEs reported and AE reporting rates per 100,000 prescriptions have increased compared with previous reporting periods for cases of addiction, death, and overdose, with a decrease in cases of pediatric exposure.

Table 6: Reporting Rates of AEs of Interest by Total Prescriptions over Time

AEs of Interest	72-Month Reporting Period 29AUG2016–28AUG2017		60-Month Reporting Period 29AUG2015–28AUG2016		48-Month Reporting Period 29AUG2014–28AUG2015		36-Month Reporting Period 29AUG2013–28AUG2014	
	AEs[a,b] n	AEs/100,000 Prescriptions (N=53,757)	AEs[a,b] n	AEs/100,000 Prescriptions (N=88,332)	AEs[a,b] n	AEs/100,000 Prescriptions (N=112,522)	AEs[a,b] n	AEs/100,000 Prescriptions (N=94,464)
Addiction	10	18.60	6	6.79	16	14.22	6	6.35
Death	549	1,021.26	359	406.42	305	271.06	414	438.26
Overdose	34	63.25	5	5.66	10	8.89	2	2.12
Pediatric Exposure	1	1.86	5	5.66	5	4.44	2	2.12

[a] Cases may have more than 1 adverse event of special interest.
[b] Reflects updates from counts and rates reported in the 60-month assessment report.

The AE of interest rates per 100,000 patients (Table 6) indicate an increase in the 72-month report compared with previous reporting periods for cases of addiction, death, and overdose, and a decrease in cases of pediatric exposure.

Table 7: Reporting Rates of AEs of Interest by Total Patients over Time

AEs of Interest	72-Month Reporting Period 29AUG2016–28AUG2017		60-Month Reporting Period 29AUG2015–28AUG2016		48-Month Reporting Period 29AUG2014–28AUG2015		36-Month Reporting Period 29AUG2013–28AUG2014	
	AEs[a, b] n	AEs/100,000 Patients (N=6,984)	AEs[a, b] n	AEs/100,000 Patients (N=11,107)	AEs[a,b] n	AEs/100,000 Patients (N=15,922)	AEs[a,b] n	AEs/100,000 Patients (N=14,772)
Addiction	10	143.18	6	54.02	16	100.49	6	40.62
Death	549	7,860.82	359	3,232.20	305	1,915.59	414	2,802.60
Overdose	34	486.83	5	45.02	10	62.81	2	13.54
Pediatric Exposure	1	14.32	5	45.02	5	31.40	2	13.54

[a] Cases may have more than 1 adverse event of special interest.
[b] Reflects updates from counts and rates reported in the 60-month assessment report.

Limitations to calculating and interpreting these reporting rates using spontaneously reported AE data include 1) existence of a report does not establish causation, 2) possible duplicate and incomplete reports may not have been removed, and 3) sponsors may not have been able to medically verify reports. Sponsors follow their own processes and procedures when it comes to safety reporting and Medical Dictionary for Drug Regulatory Activities (MedDRA) coding. Increases in rates over time may be influenced by recent focus on the opioid epidemic in the US,

which could have stimulated greater spontaneous reporting. Reporting rates may be impacted by proactive outreach made to patients and prescribers related to REMS requirements and other patient assistance services. Additionally, follow-up information may be obtained by Sponsors on retrospective cases that change their category of interest and that is not accounted for in this report. Further, some cases reference fentanyl, but do not include information on the specific formulation, so the TRIG is unable to confirm that the case is in reference to a TIRF product, versus a product covered under a different REMS (e.g., fentanyl patch), or illicit fentanyl. The rates are based only on reported cases; true incidence rates cannot be calculated, and these data should be interpreted with caution.

Cases of Addiction

Of the 10 cases classified as addiction in the most recent reporting period, 2 cases had an outcome of "not recovered/not resolved" at the time of the data cut off (28 August 2017); and 7 cases had an outcome of "unknown." The remaining case had an outcome of death; this case was reported by an attorney who was bringing a legal suit against a manufacturer. Of the 10 cases reported as addiction, the potential causality was determined as related for 6 cases, possibly related for 1 case, not related for 2 cases, and the last case had insufficient information for any determination. Two cases were cases of addiction and overdose, one of which resulted in death.

Cases of Death

There were 549 reports of death; more than 130 of these cases noted hospice care. Of the 549 reports, 355 cases did not include enough information to allow for an assessment of potential causality. A total of 187 death cases were determined to be not related to the TIRF medication.

Of the total 549 reports, 5 deaths had a causality possibly related to the TIRF product. Two additional reported deaths were determined to be related to the TIRF medication in which the prescribing physician confirmed inappropriate use in the case narrative.

Of the 24 cases that included more than one AE of interest, 1 was categorized as addiction, overdose, and death. The remaining 23 cases are cases of overdose and death. Twenty-one of the 23 cases of overdose and death were from a single consumer source that reported deaths of suspected overdose.

The total number of deaths in the 72-month report increased notably compared to the previous annual report. This increase parallels the overall upsurge of fentanyl deaths reported nationally. It is difficult to distinguish TIRF products from illicit fentanyl postmortem [Warner 2016] and, as noted above, some case reports reference fentanyl but do not include information on the specific formulation, so it is not possible to confirm that a TIRF product was administered. The increase in reported deaths may have been influenced by the recent focus on the opioid epidemic in the US, which could have stimulated greater spontaneous reporting. Spontaneous reporting rates may also be affected by proactive outreach made to patients, caregivers, and prescribers related to TIRF REMS requirements and other patient assistance services.

Cases of Overdose

There were 34 overdose cases reported during the 72-month reporting period. A total of 24 of these cases had an outcome of death, in which 2 cases had a causality reported as related, and 22 cases had insufficient information with no potential causality. Of the 10 remaining overdose

cases, 8 had an unknown outcome and 2 had not recovered or resolved. Eight cases were possibly related or related, and 2 had insufficient information with no potential causality. A total of 23 cases were flagged as overdose and death, 1 case was designated as death, overdose, and addiction, and 1 case was designated as addiction and overdose. As noted above, 21 of these reports were from a single consumer source that reported deaths of suspected overdose.

Case of Pediatric Exposure

During the 72-month reporting period, 1 pediatric case was reported with an outcome of "unknown." The report included the MedDRA preferred terms of "Product use in unapproved indication" and "Drug administered to patient of inappropriate age."

2.4.3. Persistency Analysis

2.4.3.1. Background

In the Acknowledgement Letter (initially received on August 4, 2015) for the 36-month report, the FDA requested an analysis of "…how many people are at risk for inappropriate conversion between TIRF medicines" by evaluating how long patients stay on one TIRF and whether they shift between TIRF products or just stop them completely.

The objectives of the persistency analysis were as follows:

1. To identify the number of patients starting on a TIRF and summarize their treatment course and change in therapy
2. To depict what treatment option the patient uses next following the discontinuation of one TIRF product, as applicable
3. To propose what duration of gap will be considered to mean that the patient has remained on treatment with a TIRF and provide a rationale for selection of that gap length

The persistency analysis was an observational retrospective cohort study that used data collected in the pharmacy network database, which contains complete outpatient TIRF prescription data collected since the inception of the REMS (March 12, 2012). The dataset used for this analysis included anonymized data for paid claims only; rejected transactions and reversed claims were not included in the analysis.

The persistency analysis included patients who had at least two TIRF product prescriptions from an outpatient pharmacy between March 12, 2012 and October 28, 2015 (observation period). Patients with only one filled TIRF prescription over the course of the entire observation period were excluded from the persistency analysis. The rationale for this exclusion is because it is unknown whether these seemingly one-time filled-prescriptions of the TIRF medicine were (1) continuing therapy (e.g., inpatient setting), (2) had discontinued treatment after one prescription or (3) had died. It is assumed that patients who filled only one prescription during the eligible period without a second prescription fill to confirm continuous use did not intend long-term TIRF therapy. Therefore, they are not considered to be "at risk" of inappropriate conversion between TIRF products.

A TIRF regimen could include >1 TIRF medicine as reflected by the fill date of the prescriptions (concurrent therapy). Prior to the conduct of the persistency analysis, an exploratory data feasibility analysis was performed to determine a grace period, by when a patient is still considered to be persistent on the regimen although a refill had not occurred by the date of end of day's supply. This gap in therapy is termed a permissive gap. By the same token, an impermissive gap means a gap in therapy where the refill occurred beyond the grace period, although it is a refill of the same regimen.

Persistency was presented as a percentage of patients who displayed continuous use of the TIRF regimen for the entire duration of the observation period, regardless of the number and duration of permissive gaps. Persistency was also analyzed using the Kaplan-Meier method, where patients who remained on the TIRF regimen at the end of the follow-up period were censored. At the patient-level, persistency was described for both first (index TIRF) and second TIRF regimen (where applicable). The analysis also divided patients into subgroups based on their prescription data available for analysis: (1) 12 to <24 months, (2) 24 to <36 months, and (3) ≥36 months.

Results: There were 26,273 unique patients in the pharmacy network database; 8,113 patients filled a one-time prescription only and were excluded from the persistency analysis. The TRIG analyzed patterns of filled prescriptions of 18,160 patients to assess persistency of TIRF therapy. The average number of months for patient observation was 32.3 months (minimum 12 months, maximum 44 months). 18,160 patients initiated an index TIRF therapy; 9,283 patients initiated a second TIRF therapy; 2,054 patients initiated a third TIRF therapy. Based on the average duration of gaps (measured in days) between fills and the average number of gaps in prescription fill patterns, exploratory feasibility analysis determined that a "permissive gap" or "grace period" of TIRF therapy is equal to 2.5 times its days' supply since a TIRF product is used on an "as needed" basis.

Persistency of index regimen at 6 months was 45.2% (n=8210/18160). The overall persistency of index regimen was 10.4% (n=1892/18160); 20.5% (n=3718/18160) of patients made a change in their index regimen to a second TIRF regimen and 69.1% (n=12550/18160) discontinued. Of the 12,550 patients who discontinued their index TIRF regimen, 44.3% (n=5565/12550) re-initiated by refilling the same regimen beyond the grace period. Although these patients used the same TIRF medicine(s) for the index and second TIRF therapy, they were deemed non-persistent by study definition with respect to the established rule of permissive gap as one of the study objectives. If disregarding the rule of permissive gap, persistency with index regimen was 41.1% (n=7457/18160).

There were 9,283 patients who initiated a second TIRF therapy; 10.5% (n=974/9283) of patients persisted with their second TIRF regimen, 25.6% (n=2378/9283) made a change in their second TIRF regimen and 63.9% (n=5931/9283) discontinued their second TIRF regimen. Of those who discontinued their second TIRF regimen, 42.6% (n=2527/5931) re-initiated the same regimen as their third regimen.

2.4.3.2. Discussion

Results of the persistency analysis described the number of patients starting on a TIRF and summarized their treatment course and change in therapy. As part of the documentation of treatment course and change in therapy, at least three lines of therapy (index, second and third regimens) used by the patients were described where applicable. This includes detailed

descriptions of the sequences of concurrent therapy and switches between TIRF medicines. Most importantly, a grace period was established for the purpose of this persistency analysis. An exploratory feasibility analysis was done to determine a reasonable grace period, since TIRF medicines are used on an "as needed" basis, and there is no external evidence to define a period within which a patient must refill a TIRF regimen in order to maintain optimal treatment effect.

With longer follow-up duration, the proportion of patients who had a change in therapy or discontinuation increased. This was anticipated because the longer the patients were on TIRF therapy, the more likely they were to have a switch or a gap in their treatment course.

Patients who discontinued an index regimen and then re-initiated the same regimen as a second regimen beyond the grace period were deemed non-persistent based on the study-established rule of impermissive gap. From the clinical perspective, the application of this impermissive gap may not be reasonable for a product to be used as needed, as these patients used the same TIRF products for both index and second regimens. However, an important point to keep in mind is that the data source does not provide any information on what treatments were given to the patients during impermissive gaps (e.g., whether patients switched to a different TIRF regimen as inpatient during a gap). Furthermore, one of the objectives of the current persistency analysis is to determine a grace period, and for this reason, the rule of impermissive gap (refill not occurring within 2.5x days' supply) was strictly applied in analyses to enforce conservative classification of the proportion of patients who were persistent.

As the ultimate objective is to determine the proportion of patients who were at risk of inappropriate conversion between TIRF products, interpretation of the persistency analysis results is therefore focused on the 20.5% (n=3718/18160) patients who made a change to their index regimen. Of the 3,718 patients, 83.0% (n=3087/3718) switched to a completely different regimen, and 9.8% (n=364/3718) added another TIRF product to their existing regimens. In theory, 19.0% (n=3451/18160) patients were at risk of inappropriate conversion.

2.4.3.3. Conclusions

Persistency with index TIRF therapy was 45.2% at 6 months based on the analysis of prescription sequences of 18,160 patients in the pharmacy network database. The overall discontinuation rate was high at 57.2% (n=10389/18160) following a patient's second regimen (reason for discontinuation unknown and could be due to death).

TIRF medicines are used on an "as needed" basis; therefore, it is possible that a patient may be prescribed a 30-day supply of medication that has stretched to cover the patient's need of pain medication for six months. In this persistency analysis, patients who appeared to have changed their index regimen by adding another TIRF medicine (classified as initiating concurrent therapy) could, in fact, have never actually used the added TIRF while remaining on the index TIRF. Therefore, without supplementary medical information, one needs to interpret results of the persistency analysis with caution.

Based on the results of the current analysis, it is estimated that in real-world practice, approximately 19% of patients change their regimen by switching to a different TIRF product.

2.4.4. Opioid Tolerance Study

2.4.4.1. Background

TIRF products are indicated for use only in opioid tolerant patients, based on concurrent regular use of another opioid medication. One REMS assessment was to conduct an opioid tolerance study. The objective of the study was to determine the proportion of unique patients dispensed an initial prescription for a TIRF product who had received a prescription for an opioid analgesic product prior to the prescription for the TIRF product. The analysis was conducted separately for patients receiving an opioid analgesic within the 7 days prior and within the 30 days prior to the initial TIRF prescription.

The study was an observational retrospective cohort study using pharmacy claims from the retail, specialty and mail order, and long-term care channels of the IQVIA Longitudinal Prescription Database (LRx). At the time of the study, the LRx database contained electronic dispensing records representing prescriptions for 86% of the outpatient retail pharmacy channel, 40-75% of specialty and mail-order prescriptions (depending on therapeutic area), and about 50% of prescriptions from long-term care pharmacies (across therapeutic areas). \

Using the LRx database, patients who filled a TIRF product prescription from an outpatient pharmacy (retail and specialty/mail order) between March 12, 2012 and October 28, 2015 (index period) were identified. Patients were excluded if they met any of the following criteria: (1) age inconsistent with TIRF product labeling (<16 years of age for Actiq® and oral transmucosal fentanyl citrate lozenge generics; <18 years of age for other products), and (2) ≥1 TIRF product prescriptions filled from a long-term care pharmacy.

An initial TIRF product prescription was defined as the date of the first prescription fill (i.e. not a refill) for a REMS-covered TIRF product during the index period. Prior prescriptions of opioid analgesic products were identified as ≥1 prescription fill for opioid analgesics within 30 days of the initial TIRF product prescription.

To calculate the proportion of TIRF product users with an opioid analgesic product fill, patients were additionally restricted to those with ≥1 prescription claim for any marketed product (not confined to opioids) in the 30 days prior to the initial TIRF product prescription. As the LRx database is open, this enrollment proxy restriction was necessary to prevent patients being classified as having no opioid history due to lack of data capture rather than true lack of a prescription. Within the subset of patients meeting this restriction, the proportion of TIRF product users who had a fill for an opioid analgesic product prior to the initial TIRF prescription was determined: overall, within the prior 7 days, and within the prior 8-30 days (patients could be counted in both groups due to refills and concurrent used of multiple opioid analgesic products).

Patients meeting the enrollment proxy restriction were considered opioid tolerant if, prior to their initial TIRF product prescription, for one week or longer they took at least: 1) 60 mg oral morphine/day, 2) 25 mcg transdermal fentanyl/hour, 3) 30 mg oral oxycodone/day, 4) 8 mg oral hydromorphone/day, 5) 25 mg oral oxymorphone/day, or 6) an equianalgesic dose of another oral opioid (e.g., 60 mg oral hydrocodone/day). The proportion of TIRF patients with days' supply consistent with the above definition of opioid tolerance was reported.

2.4.4.2. Results

A total of 27,320 unique patients received an initial outpatient TIRF product prescription between March 12, 2012, and October 28, 2015 and were captured in the LRx database. Due to standard practice LRx quality control procedures, 1,815 (6.6%) patients were removed. There were 183 patients who were excluded because their age was inconsistent with TIRF labeling.

There were 21,286 (84.1%) patients who met the enrollment proxy restriction of having ≥1 prescription claim for any marketed product (not confined to opioids) in the 30 days prior to the initial TIRF product prescription fill. Of them, 18,280 (85.9%) unique patients received an outpatient opioid analgesic prescription in the 1-30 days prior to the TIRF product prescription. Within that period, 7,333 patients (34.4%) received an opioid analgesic in the 1-7 days prior, 16,096 patients (75.6%) received an opioid analgesic in the 8-30 days prior, and 5,149 (24.2%) had a fill in both prior use windows. Overall, 12,406 patients (58.3%) were considered opioid tolerant.

2.4.4.3. Conclusions

A total of 21,286 patients were dispensed an initial prescription for a TIRF product in the outpatient setting. Of patients meeting the enrollment proxy restriction, 85.9% unique patients received an outpatient opioid analgesic prescription in the 1-30 days prior to the TIRF product prescription and 58.3% of patients were considered opioid tolerant.

The largest strength of this study was that it was conducted in a large database representing prescriptions from 86% of the retail and specialty/mail order channels in the US. However, the results should be interpreted in the context of the following limitations: (1) Medication use patterns from claims data are always estimates. For example, there may be misclassification of opioid analgesic use and opioid tolerance if patients did not take prescriptions exactly as prescribed or when prescriptions were dosed “as needed”, (2) Lack of hospital data in the LRx means that inpatient opioid analgesic use (that healthcare providers may have been aware of) was not captured, potentially causing an underestimation of opioid tolerance for recently hospitalized patients, (3) Similarly, the LRx does not capture outpatient injections, (4) Concurrent use of multiple opioid products could not be distinguished from product switching which may have led to overestimation of opioid tolerance in cases where a patient was down titrated, and (5) Proportion of opioid tolerant patients may vary across studies depending on key design factors such as the stringency of the opioid tolerance definition and the type of enrollment proxy used (both of which have varied in prior tolerance analyses in this database).

The results of this study, while generalizable to the outpatient setting, do not generalize to inpatient settings as this information was not available in the dataset. Nevertheless, with 86% of patients receiving an outpatient prescription for an opioid analgesic prior to the use of a TIRF REMS product, results suggest that the TIRF REMS Access Program may have been successful in limiting the use of TIRF REMS products in opioid naïve patients.

2.5. Knowledge, Attitude, and Behavior Surveys of Stakeholders

Ongoing education of all stakeholders is a hallmark of the REMS TIRF Access Program, with evidence supporting success in this regard. Education starts with the mandated Knowledge Assessment, Medication Guides for patients, and specific materials for all stakeholders. Results

of the annual KAB surveys show a high level of understanding about the risks of abuse, addiction, and overdose among patients, prescribers, and pharmacies, which has been maintained or improved over time.

2.5.1. Patient KAB Survey Results

The questions and statements in the survey were constructed to test patient or caregiver understanding of the following REMS key risk messages:

1. TIRF medicines can cause life-threatening breathing problems that can lead to death.
2. Patients should not take TIRF medicines if they are not opioid tolerant.
3. TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4. Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5. Patients should never give TIRF medicines to anyone else even if they have the same symptoms.
6. TIRF medicines should be stored in a safe place away from children and properly disposed.

The most recent survey launched on 02 August 2017 and closed on 18 October 2017. Patients who were passively enrolled in the TIRF REMS Access Program and had received a TIRF medicine in the previous 4 months (120 days) were invited to participate. Out of 429 patients/ caregivers who accessed the survey, 320 (74.6%) respondents met the eligibility criteria, and 310 (96.9%) of those who were eligible completed the survey, exceeding the target of 300 completed surveys.

At the request of the FDA, questions (Questions 36 and 37) were added for the current survey to assess if signing the current PPAF was seen as a barrier to obtaining a prescription for a TIRF medicine by the patient/caregiver. Of the 15 respondents who answered "No" to Question 36 regarding whether they had signed a PPAF, all indicated they were never given a form to sign. Question 37 asked all 310 respondents who completed the survey whether signing or being asked to sign a PPAF was a barrier to obtaining a TIRF medicine prescription. About one quarter of respondents (27.1%) answered "Yes", about half (45.5%) answered "No", and 27.4% selected "I don't know."

The overall knowledge score of 86.3 (95% confidence interval [CI]: 85.1–87.5) for the survey indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score was ≥86.0 for 5 of the 6 key risk messages (1, 2, 4, 5, 6) and was 74.4 for Key Risk Message 3. Of the 22 questions/items included as part of key risk messages, 18 items had a correct response rate ≥80%, and 4 items within Key Risk Message 3 had a correct response rate below the 80% threshold.

Within Key Risk Message 3, correct response rates for 4 items were <80% as follows:

Question 10: For which of the following conditions should you use a TIRF medicine?

- Item 10d: Pain after surgery ("No") correct response rate 68.4% (64.2–70.3% in 5 previous surveys)

- Item 10e: Long-lasting pain not from cancer, like arthritis joint pain ("No") correct response rate 48.1% (21.9–43.9% in 5 previous surveys)

Question 12: Please answer True, False, or I don't know for each of the following statements.

- Item 12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (correct response "True") correct response rate 43.2% (34.1–42.7% in 5 previous surveys)

Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

- Item 13b: It is OK for patients to take TIRF medicines for headache pain (correct response "False") correct response rate 72.6% (67.4–74.8% in 5 previous surveys)

The correct response rates over time, from the 12-month through the 72-month KAB survey, indicate that knowledge and understanding of the key risk messages has generally remained stable over time. The low scoring items mentioned above had a consistently low correct response rate across all patient/caregiver KAB surveys conducted.

For all key risk messages except Key Risk Message 4, there was a higher correct response rate in respondents who indicated they received and read the Medication Guide and in those who indicated they understood all or most of the Medication Guide compared to those who did not receive or read it.

2.5.2. Prescriber KAB Survey Results

The 72-month KAB survey for prescribers launched on 02 August 2017 and closed on 29 October 2017. Participants were prescribers who enrolled in the TIRF REMS Access Program who had prescribed a TIRF medicine in the last 6 months. A total of 273 respondents accessed the survey, 178 of 273 (65.2%) prescribers met the eligibility criteria, and of the eligible prescribers, 154 (86.5%) completed the survey.

The survey was designed to test the prescribers' understanding of the following 4 key risk messages:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

The overall knowledge score of 89.6 (95% CI: 88.0–91.3) for the survey indicates a high percentage of respondents demonstrated understanding of the key risk messages. The average knowledge score was >87 for all key risk messages. Of the 38 questions/items included as part of

key risk messages, 31 questions/items had a correct response rate >80% and 7 questions/items had a correct response rate below the 80% threshold.

Within Key Risk Message 1, the correct response rates for 3 items of Question 13 were <80% as follows:

Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least

- Item 13a: 8 mg oral hydromorphone/day; (True) correct response rate 77.3% (68.5%-72.9% in 4 previous surveys)
- Item 13e: 25 mg oral oxymorphone/day; (True) correct response rate 79.2% (69.9%-79.6% in 4 previous surveys)
- Item 13f: An equianalgesic dose of another oral opioid; (True) correct response rate 70.1% (59.0%-67.7% in 4 previous surveys)

Within Key Risk Message 2 questions, the correct response rates for 3 items were <80%:

Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

- Item 6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time; (False) correct response rate 79.2% (60.0%-77.2% in 4 previous surveys)

Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.

- Item 9e: Chronic non-cancer pain; (No) correct response rate 79.2% (54.3%-78.2% in 5 previous surveys)

Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.

- Item 20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine; (False) correct response rate 74.0% (57.9%-76.5% in 5 previous surveys)

Within Key Risk Message 3 correct response rate for 1 item for Question 22 was <80% as follows:

Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.

- Item 22e: Hypothyroidism; (False) correct response rate 72.1% (78.9% in 1 previous survey).

When comparing correct response rates from the 12-month KAB survey through the 72-month KAB survey, prescriber knowledge and understanding of the key risk message questions has generally remained stable or improved over time.

2.5.3. Pharmacist KAB Survey Results

The pharmacist survey launched on 02 August 2017 and closed on 18 October 2017. Participants were recruited from pharmacies enrolled in the TIRF REMS Access Program as of 17 July 2017 that had dispensed a TIRF medicine in the last 6 months. A total of 676 pharmacists accessed the survey, 325 of 676 (48.1%) pharmacists met eligibility criteria, and of the eligible pharmacists, 308 (94.8%) completed the survey, exceeding the target of 300 completed surveys.

The survey tested the pharmacists' understanding of the following 4 key risk messages of the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

The overall knowledge score of 84.9 (95% CI: 83.4–86.4) for the survey indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score for each of the key risk messages was ≥82.8 for 3 of the 4 key risk messages and was 76.6 for Key Risk Message 2. The lower average knowledge score for Key Risk Message 2 reflected 3 linked questions/items (described below) with relatively low correct response rates of 48.1-66.9%.

Of the 36 questions/items included as part of key risk messages, 23 items of the key risk messages had correct response rates at or above the desired threshold of >80%. The 13 items with correct response rates below this threshold were as follows:

2.5.3.1. Key Risk Message 1

Item 5c: *According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those who have no known contraindications to the drug fentanyl but are not currently taking around-the-clock opioid therapy.*

- Item 5c (False) correct response rate was 78.2% (76.0–82.4% in 4 previous surveys).

Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

(True for all) correct response rates for 5 of the 6 items were <80%:

- Item 11a: 8 mg oral hydromorphone/day; 74.7% (74.5–79.0% in 4 previous surveys)
- Item 11c: 30 mg oral oxycodone/day; 76.3% (71.3–77.7% in 4 previous surveys)

- Item 11d: 25 mcg transdermal fentanyl/hour; 77.6% (72.0–79.6% in 4 previous surveys)
- Item 11e: 25 mg oral oxymorphone/day; 70.8% (71.0–73.4% in 4 previous surveys)
- Item 11f: An equianalgesic dose of another oral opioid; 64.0% (59.0–65.1% in 4 previous surveys)

2.5.3.2. Key Risk Message 2

Item 6a: *According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.*

- Item 6a (False) correct response rate was 66.9% (61.9–69.1% in 4 previous surveys)

Item 6b: *According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.*

- Item 6b (False) correct response rate was 79.2% (74.0–82.1% in 4 previous surveys)
- Item 6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.
- Item 6c (True) correct response rate was 48.1% (41.2–41.9% in 2 previous surveys)

For Question 9 the correct response rate for 1 of the 5 items <80%:

Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?

- Item 9c: Chronic non-cancer pain; (No) correct response rate was 53.6% (43.7–50.9% in 4 previous surveys)

2.5.3.3. Key Risk Message 3

For Question 8 the correct response rate for 1 of the 2 items <80%:

Question 8: Which of the following are risk factors for opioid abuse?

- Item 8a: A personal history of psychiatric illness; (Yes) correct response rate was 79.2% (71.0%-77.7% in 4 previous surveys)

For Question 13, correct response rates for 2 of the 6 items were <80%:

Question 13: Which of the following risks are associated with the use of TIRF medicines?

- Item 13e: Hypothyroidism; (False) correct response rates 73.7% (84.0% in 1 previous survey)
- Item 13f: Infection; (False) correct response rates 76.3% (89.3% in 1 previous survey)

In general, the pharmacist survey results show an overall trend over time toward maintaining or increasing pharmacist knowledge of key messages.

2.5.4. KAB Survey Conclusions

Overall, the 72-month survey shows a high level of patient, prescriber, and pharmacist understanding of key risk messages based on the REMS goals has been consistent over time. The findings also indicate that additional educational efforts may be needed in the following areas: patient knowledge related to conditions for use of a TIRF medicine and stopping a TIRF medicine when stopping their maintenance opioid pain medicine; prescriber knowledge related to TIRF medicine use when stopping around the clock opioid pain medicine and the definition of opioid tolerant; and pharmacists' knowledge related to indications for TIRF medicines and safe use of TIRF medicines by patients also using around the clock opioid pain medicines.

3. CONCLUSIONS FROM THE ASSESSMENT DATA

Note to readers: the following section is the same as Section 1.7.5 in the Overview.

The key findings from the TIRF REMS Access Program evaluations are:

- The total number of patients receiving TIRF medications and TIRF medication prescriptions has declined since the initiation of the program, and this trend continues in the most recent reporting cycle
- TIRF prescriptions are subject to a safety adjudication by the TIRF REMS Access Program, which helps ensure that REMS requirements are met
- The non-compliance program effectively identifies and investigates stakeholders who do not follow REMS procedures. The rate of confirmed non-compliance events has decreased over the past four annual reports, indicating that prescribers and pharmacies are compliant with REMS requirements. Over the course of the program, 11 prescribers have been permanently deactivated from prescribing TIRF medicines
- According to RADARS surveillance data, the number of AEs of interest, including overdose, death, and pediatric exposure, is very low, averaging <1 per quarter since 2010
- Aggregate spontaneous reporting of AEs collected by the TRIG confirms that accidental exposure in children is extremely rare
- Spontaneously reported AEs do not show evidence of inappropriate conversion between TIRF products. A persistency analysis found that 19% of patients switched from 1 TIRF regimen to another and were therefore potentially at risk of inappropriate conversion
- Results from KAB surveys for all stakeholders show a high level of understanding of most key risk messages that has been sustained or increased over time.

4. ASSESSMENT GAPS AND LIMITATIONS

Note to readers: the following section is the same as Section 1.8 in the Overview.

Post-marketing safety surveillance based on AEs spontaneously reported to pharmaceutical manufacturers has several limitations, including possible multiplicity (a single event may be

reported by several different sources); frequently unknown or misattributed cause of death, especially among patients at or near end of life; and frequent inaccuracy in terms of concomitant medications, both prescribed and illicit. For the TIRF products, some spontaneously reported cases refer to fentanyl but do not include information on the formulation, so that involvement of a TIRF medication cannot be confirmed.

Currently, spontaneous AE reporting is the primary source of REMS assessment data for capturing inappropriate use such as TIRF prescriptions given to non-opioid-tolerant patients or inappropriate conversion from one TIRF medication to another. These incidents do not, however, necessarily lead to AEs that would be captured by spontaneous reporting, nor would they be clearly evident in the event narratives. Additional types of studies are needed (and are being implemented or considered by the TRIG sponsors) to provide better monitoring of TIRF use in non-opioid-tolerant patients and of inappropriate conversions.

The RADARS report also relies on spontaneous reporting to the Poison Center Program for its data on intentional and unintentional exposure, pediatric exposure, emergency department visits and hospitalizations, and major medical outcomes and death. As the RADARS authors note, patients and family members do not always call a poison center to report an event. Thus, the number of events in this analysis may be underestimated, although usually representative of trends over time.

However, the very low numbers of reported events with TIRF products pose a different problem. These numbers are so low that the pre- and post-REMS trends, compared with other, more-widely used opioids with greater numbers of reported events, may be of limited utility. This point is made by the RADARS authors, who note a greater possibility of false positive findings in the trends analyses when the absolute numbers are so low.

The KAB surveys of patients, prescribers, and pharmacies enrolled in the TIRF REMS Access Program show generally high levels of understanding of key risk messages, but they also indicate consistent sub-par performance by prescribers and pharmacies on specific questions regarding the definition of opioid tolerance and the proper use of TIRF drugs in the context of maintenance opioid treatment for pain relief. The TIRF sponsors agree that additional education with updated wording to clarify messages is required on these topics and conclude that the surveys themselves require revised text to more precisely identify areas of educational need.

5. PROPOSED REMS PROGRAM CHANGES

Note to readers: the following section is the same as Section 1.9 in the Overview.

Throughout the life of the TIRF REMS Access Program, changes and improvements have been continuously made in collaboration with FDA and in response to the Agency's review and feedback of the annual assessment reports. New proposed TIRF REMS program changes include:

- Working with FDA to update educational materials to reinforce the messages not clearly understood as evidenced by low-scoring KAB questions, such as prescriber understanding of opioid tolerance and prescriber and pharmacist understanding of the need to start TIRF treatment only if around-the-clock opioid therapy is ongoing and to stop TIRF treatment if opioid maintenance is discontinued

- Upon identifying changes to the educational materials, align the Knowledge Assessment to be consistent with the education materials
- Updating the non-compliance protocol in accord with FDA recommendations so that prescribers will be flagged at first occurrence of patient enrollment without a PPAF submitted within 10 days, and streamlining the notification and warning process so that the first non-compliance offense results in a notice, the second in a warning, the third in suspension from the program, and the fourth in permanent deactivation from prescribing TIRF products
- Revising the PPAF to include a prescriber attestation to confirm that the patient is opioid tolerant
- Adding attestation language to all pharmacy enrollment forms to allow the program to further audit pharmacies for REMS compliance
- Increase surveillance of prescriber non-compliance with the goal of reducing the possibility of patients being enrolled without a PPAF

6. NEW AND UPDATED ASSESSMENTS

Note to readers: the following section is the same as Section 1.10 in the Overview.

In addition to the activities and plans outlined in the preceding section, the TRIG sponsors plan the following assessments to improve the evaluation of the TIRF REMS effectiveness:

- Working with FDA to develop two separate studies (Drug Involved Mortality data and Optum/Humedica) to assess the risk of accidental exposure of TIRF products to children, which would supplement the current spontaneous reporting of pediatric exposure events
- An IQVIA study was conducted to evaluate the occurrence of prescribing to opioid-tolerant and opioid-non-tolerant patients. TRIG is now working with FDA to validate the study algorithm defining opioid tolerance for broader use in identifying opioid-tolerant patients appropriate for TIRF administration.
- Working with FDA to plan studies that involve detailed review of medical records. These will include analysis of fatal and non-fatal overdose in opioid tolerant versus opioid non-tolerant TIRF users.

7. CONCLUSIONS

Overall, the TIRF REMS Access Program is generally meeting its goals of ensuring safe and appropriate use of TIRF products, and the TRIG is working constantly within the industry and with the FDA to refine the program as needed. A comprehensive array of evidence-based metrics supports the elements and execution of the REMS, and lessons learned from these assessments and FDA reviews are guiding ongoing improvement.

TIRF products offer a means for appropriate patients to receive fentanyl in accessible formulations. These medicines are critically needed by cancer patients, many of them at end of

life, whose spontaneous breakthrough cancer pain is so severe and disabling that no other form of pain management provides appropriate relief. TIRF products should be prescribed in the context of around-the-clock opioid therapy, which ensures that the patients are opioid-tolerant and can safely receive appropriate doses of fentanyl.

TIRF products are the only medicines specifically indicated for the treatment of BTCP. BTCP can be severe and debilitating, having an enormous impact on the lives of a substantial number of cancer patients. For these patients, the REMS program enables continued access to urgently needed TIRF medicines within a safe and carefully monitored framework of treatment. Recommendations for further improvements to the program should not negatively affect this access.

The TIRF REMS Access Program was initiated in the context of a growing opioid crisis. In the 6 years since the program began, patient enrollment and prescription volume have declined dramatically. The prescription opioid market has changed as public perception and medical practice have changed.

The TIRF REMS Access Program continues to evolve in response to this changing environment. Progress has been made in educating prescribers, pharmacists, and patients about appropriate use of TIRF medicines. Although RADARS surveillance reporting shows a very low incidence of death, overdose, and pediatric or other inadvertent exposure to TIRF medicines over the life of the REMS program, the TRIG continues to advance its efforts to evaluate and mitigate risk. In collaboration with FDA, the TRIG has generated additional studies to better understand the risk of inappropriate conversion and of overdose in opioid-tolerant and non-tolerant patients. Further knowledge is needed to fully quantitate the risk of pediatric exposure, and the TRIG is evaluating data sources for assessment in this area. Work is also underway toward developing a validated algorithm that will help healthcare professionals define opioid tolerance.

The TIRF REMS Access Program has demonstrated the ability to educate prescribers and pharmacists about the appropriate use of TIRF medicines. The TRIG sponsors will work with FDA to ensure that the program continues to build on the progress made and to address areas of need.

The remainder of this document will focus primarily on a more detailed presentation of the program assessment data.

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APPENDIX A. THE TIRF REMS

Initial REMS approval: 12/2011

Most recent modification: 08/2017

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

Reference ID: 4148977

I. 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.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment*).

ii. Complete and sign the *Prescriber Enrollment Form*. In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.

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

e) I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other regardless of route of administration, and that conversion may result in fata overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreemen Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS

Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.

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

3) I understand that TIRF medicines are not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.

4) I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; 60 mg oral hydrocodone/day; or an equianalgesic dose of another opioid daily.

5) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

6) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

7) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

8) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not

been prescribed can result in a fatal overdose.

D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.
4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.
6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8) I will store my TIRF medicine in a safe place, out of reach of children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.
10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

- *TIRF REMS Access Prescriber Program Overview*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement Form*
- *TIRF REMS Access Patient and Caregiver Overview*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), 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. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the TIRF REMS Access program and is appended.

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

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

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

   c. For the purposes of this REMS, there are different requirements for :

      - **Outpatient Pharmacies**

        i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e., chain stores) in the TIRF REMS Access program.

        ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

        iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

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

   d. ***Chain and Independent Outpatient Pharmacy(s):***

      The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

      i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment.*

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method

of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

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

Note: The *'or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. ***Closed System Outpatient Pharmacies*:**

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment.*

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understanc that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversior recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivatec from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

   a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

   b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

   c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

   d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

   e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

   f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

   g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

   h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy or Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

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

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2 respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:
   i. The patient has not filled a prescription for more than six (6) months.
   ii. The PPAF has expired.
   iii. The patient is deceased.
   iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.
2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:
   a. Review the distributor TIRF REMS Access program materials
   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:
      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.
      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e., EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.
      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance

investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e., active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access

program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B. PRESCRIBER KNOWLEDGE ASSESSMENT

Transmucosal Immediate Release Fentanyl (TIRF) REMS
Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12-year-old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

Question 3
Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?
Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above

Question 4
A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?
Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5
A patient is starting titration with a TIRF medicine. What dose must they start with?
Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying
B. persistent cancer pain.
C. The dose that the prescriber believes is appropriate based on their clinical experience. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6
A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?
Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant. Inform patients that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain or acute pain in the emergency department.
B. Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine.
C. Instruct patients to never share their TIRF medicine with anyone else, even if that person
D. has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option
A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative DEA Number Chain ID (if applicable)

Reference ID: 4148977 DEA Number or Chain ID:_____

APPENDIX C. PATIENT-PRESCRIBER AGREEMENT FORM (PPAF)

The TIRF REMS Access Program: Patient-Prescriber Agreement Form

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that TIRF medicines are not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.
4. I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; 60 mg oral hydrocodone/day; or an equianalgesic dose of another opioid daily.
5. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
6. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
7. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
8. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Page 1

Reference ID: 4148977

The TIRF REMS Access Program: Patient-Prescriber Agreement Form

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place out of reach of children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Prescriber Name* (please print): _____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

The TIRF REMS Access Program: Patient-Prescriber Agreement Form

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

APPENDIX D. NON-COMPLIANCE PROTOCOL

TIRF REMS ACCESS PROGRAM NON-COMPLIANCE PROTOCOL

Version ~~7.0~~7.1

February 15,~~,~~ 201~~7~~8

Revision History

Version #	Date	Author	Description of Changes
1.0	February, 2012	Meagan Sampogna	Initial Release

2.0	October 10, 2012	Laura Baloun	• Added Revision History
			• Removed 'Draft-Review Required' Watermark
			• Added Sub-Sections to Section 5 (previously a separate document)
			  ○ Added 5.1 – Index of Scenarios
			  ○ Added 5.2 – Severity Reference
			  ○ Added 5.3 – Corrective Action Reference
			  ○ Added 5.4 – Monitoring Frequency Reference
			• Updated Scenario Numbering in Section 5.1
			• Revised Notices Measurement to clarify 2 Notices in 60 days = 1 Warning

3.0	November 2, 2012	Laura Baloun	• Revised Section 5.3, Reference – Corrective Actions to include review of multiple non-compliance events for a stakeholder to see if moving to the next level is warranted • Correct title of Section 5.4, Reference – Monitoring Frequency Guidelines

3.1	March 15, 2013	Laura Baloun	• Corrected misspellings throughout document
			• Revised Section 2 – Removed reference that process flow will be revised upon agreement of Protocol
			• Revised Section 2 - Non-Compliance Process Flow
			• Removed reference that Non-Compliance letters need to be developed from Section 4
			• Revised Section 5.1 – Non-Compliance Scenarios
			  ○ Revised the monitoring tool in Pharmacy Scenario 2 and Wholesaler/Distributor Scenario 1
			  ○ Revised Pharmacy Scenario 3

Version #	Date	Author	Description of Changes
			to be specific to suspended and deactivated stakeholders ○ Revised language in Pharmacy Scenarios 4, 5 & 6 for clarify ○ Added a new Pharmacy Scenario for altered claims ○ Revised Wholesaler/Distributor Scenario 1 to be specific to suspended and deactivated stakeholders ○ Revised language in Wholesaler/Distributor Scenario 2 for clarity ○ Revised Prescriber Scenario 1 to be specific to suspended and deactivated stakeholders ○ Revised language in Prescriber Scenario 2 for clarity ○ Re-defined 'timely manner' in Prescriber Scenario 2 ○ Revised language in Closed System Pharmacy Scenario 1 for clarify ○ Added a Patient non-compliant scenario ○ Added an enrollment monitoring scenario for all stakeholders • Revised Section 5.4 – Reference – Monitoring Frequency Guidelines ○ Clarified new report requests will be handled via the Change Management Process ○ Changed 'Sponsor Data' to 'Sponsor Reporting' ○ Changed frequency of Sponsor Reporting from quarterly to every Non-Compliance Review Team Meeting and as needed ○ Changed frequency of Escalation Log from daily to every Quality Management Workstream meeting and as needed

Version #	Date	Author	Description of Changes
3.2	5/21/13	Laura Baloun	• Revised Section 5.1 – Non-Compliance Scenarios ○ Removed Pharmacy Scenario 4
4.0	5/24/13	Laura Baloun	Accepted all changes from versions 3.1 and 3.2
4.1	8/7/13	Laura Baloun	Added Section 6 – Non-Compliance Assessment Reporting
5.0	8/8/13	Laura Baloun	• Accepted all changes from version 4.1 • Corrected page numbers
5.0	8/15/13	Laura Baloun	• Approved by TRIG via vote during the 8/15/13 Program Status Call Meeting
5.1	12/17/13	Laura Baloun	• Revised Section 5.1 – Non-Compliance Scenarios ○ Revised Prescriber Scenario 2 definition for 'complete PPAF on file in a timely manner' • Revised Section 5.3 – Reference – Corrective Action ○ Change 'annually' to 'within 12 months'
6.0	12/19/13	Laura Baloun	• Accepted all changes from version 5.1
6.0	12/23/13	Laura Baloun	• Approved via TRIG e-mail vote
6.1	12/5/13	Amanda Bulkley	• Revised Section 5.1 – Non-Compliance Scenarios ○ Added Pharmacy Scenario 4: Pharmacy no longer has a valid DEA. ○ Added Prescriber Scenario 3: Prescriber no longer has a valid, schedule II DEA. ○ Added Prescriber Scenario 4: Prescribed TIRF medicines to an opioid non-tolerant individual. ○ Added Prescriber Scenario 5: Inappropriate conversions between TIRF products • Revised Section 5.2 – Severity Inclusion of language for repeat offenders when determined amount of time is reached without any suspected non-compliance

Version #	Date	Author	Description of Changes
			activity • Revised Section 5.3 – Corrective Action ○ Inclusion of language for repeat offenders when determined amount of time is reached without any suspected non-compliance activity ○ Grammatical corrections
7.0	10/26/15	Amanda Bulkley	• Accepted all changes from version 6.1
7.0	10/29/15	Amanda Bulkley	• Approved via TRIG e-mail vote
7.1	02/15/18	Amanda Bulkley	• Revised Section 5.1 – Non-Compliance Scenarios ○ Added Pharmacy Scenario 8: Pharmacy sold, loaned or transferred TIRF medicine inventory ○ Revised Prescriber 2 scenario to reduce threshold of patients enrolled without a PPAF from 5 to 1 • Revised Section 5.2 – Severity to align with changes to Corrective Action for repeat offenders • Revised Section 5.3 – Corrective Action ○ Removed reference to a first level of Notice for non-compliance ○ Removed reference to a second Notice, Warning and Suspension for repeat offenders of non-compliance. ○ Redefined Severity of Corrective Action

TABLE OF CONTENTS

1. BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, especially for opioid-tolerant patients experiencing cancer breakthrough pain (BTP). Transmucosal immediate release fentanyl (TIRF) medicines are short-acting opioid products that have a rapid onset and relatively short duration of action and are designed for the treatment of episodes of BTP in opioid-tolerant patients with chronic cancer pain.

On December 28, 2011, the Food and Drug Administration (FDA) approved a single, shared Risk Evaluation and Mitigation Strategy (REMS) for TIRF products. The shared system strategy, called the TIRF REMS Access program, is used by all sponsors of TIRF products and is designed to ensure access to important medications for appropriate patients.
The TIRF REMS Access program is in place to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

a. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

b. Preventing inappropriate conversion between fentanyl products.

c. Preventing accidental exposure to children and others for whom it was not prescribed.

d. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

Compliance with the TIRF REMS Access program ("program") is necessary in accordance with the appropriate use of TIRF products and proper patient selection. The TIRF REMS Access program includes a continuous evaluation process of compliance to the program. Any deviation

from program procedures is evidence of non-compliance and may result in corrective measures, such as a warning, suspension or program deactivation.

2. GOALS AND OBJECTIVES

The goal of the non-compliance protocol is to ensure that a system is in place to identify and investigate stakeholder non-compliance with the TIRF REMS Access program by monitoring possible program deviations detected through program reporting and spontaneous events identified by the program.

Suspected non-compliance is defined as an instance when it is believed that a stakeholder is not following a program requirement. Suspected non-compliance scenarios may be detected through standard program reports, spontaneous reports identified via the program's call center or vendor/sponsor reported events. A suspected non-compliant event is deemed compliant in the event the information presented on a stakeholder scenario does not clearly identify or support that a program deviation has occurred and/or no evidence of the program goals not being met are present.

A confirmed non-compliant event is when the information presented clearly indicates that a program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified. Confirmation of a non-compliant stakeholder act will typically occur after further investigation has been completed and supportive data has been reviewed and presented to the TIRF REMS Access Non-Compliance Review Team.

The objectives of this non-compliance protocol are to:

- Describe the purpose and activities of the non-compliance Review Team
- Describe the purpose and activities of the non-compliance Working Group
- Describe the process to identify program non-compliance
- Outline an index of possible scenarios of non-compliance
- Identify data sources to review for suspected non-compliant events
- Describe suggested actions taken once non-compliance is confirmed
- Describe the process to monitor program deviations and occurrences of non-compliance

3. NON-COMPLIANCE REVIEW TEAM AND WORKING GROUP RESPONSIBILITY

A TIRF REMS Access Non-Compliance Review Team ("Review Team") will be created composed of membership from the TRIG Sponsors. The Review Team will be responsible for review, escalation, and decision-making of all non-compliance cases, and ensure corrective measures are applied when necessary.

The responsibilities of the Review Team may not be delegated or transferred to other parties without prior consent of the TRIG sponsors. If the need arises, the Review Team shall have the authority to consult external advisors, experts, or consultants, in order to effectively assess and process cases of program non-compliance. If it is determined that a program modification may be warranted due to cases of non-compliance, the Review Team may need to consult with the

FDA for their review and approval of any changes impacting the REMS submission. Any proposed program modifications must be approved by the TRIG prior to implementation. The Review Team will meet regularly to discuss all issues of non-compliance and/or program modifications, at a frequency interval defined by the TRIG sponsors. The Review Team will consist of members with expertise from various specialties, which may include:

1. Regulatory Affairs
2. REMS specialist
3. Project Management
4. Legal
5. Quality Assurance
6. Commercial
7. Drug Safety and IT

Working practices will be developed to describe when the TRIG sponsors would participate in Review Team discussion in connection with potential or actual major deviations from the REMS program.

A Non-Compliance Working Group ("Working Group") will be created from program staff and will be responsible for collecting data and preparing reports for the Review Team, in compliance with Privacy Health Information (PHI) regulations. The Working Group will consist of program agents who have been working with and/or trained on the TRIG non-compliance protocol, as well as have background necessary to evaluate data and make objective decisions on instances of non-compliance, based on the data available.
The functions of the Working Group will be to:

1. Review reports, call center logs or audit report data to identify potential incidences of non-compliance
2. Conduct further investigation as needed to clarify the potential incident and identify root cause of deviation
3. Evaluate compliance with the TIRF REMS program stakeholder business rules
4. Respond to identified events of non-compliance in accordance with the established business rules. Propose solutions and actions for confirmed non-compliance events that are not addresses by such business rules.
5. Prepare reports for review and approval by the Review Team

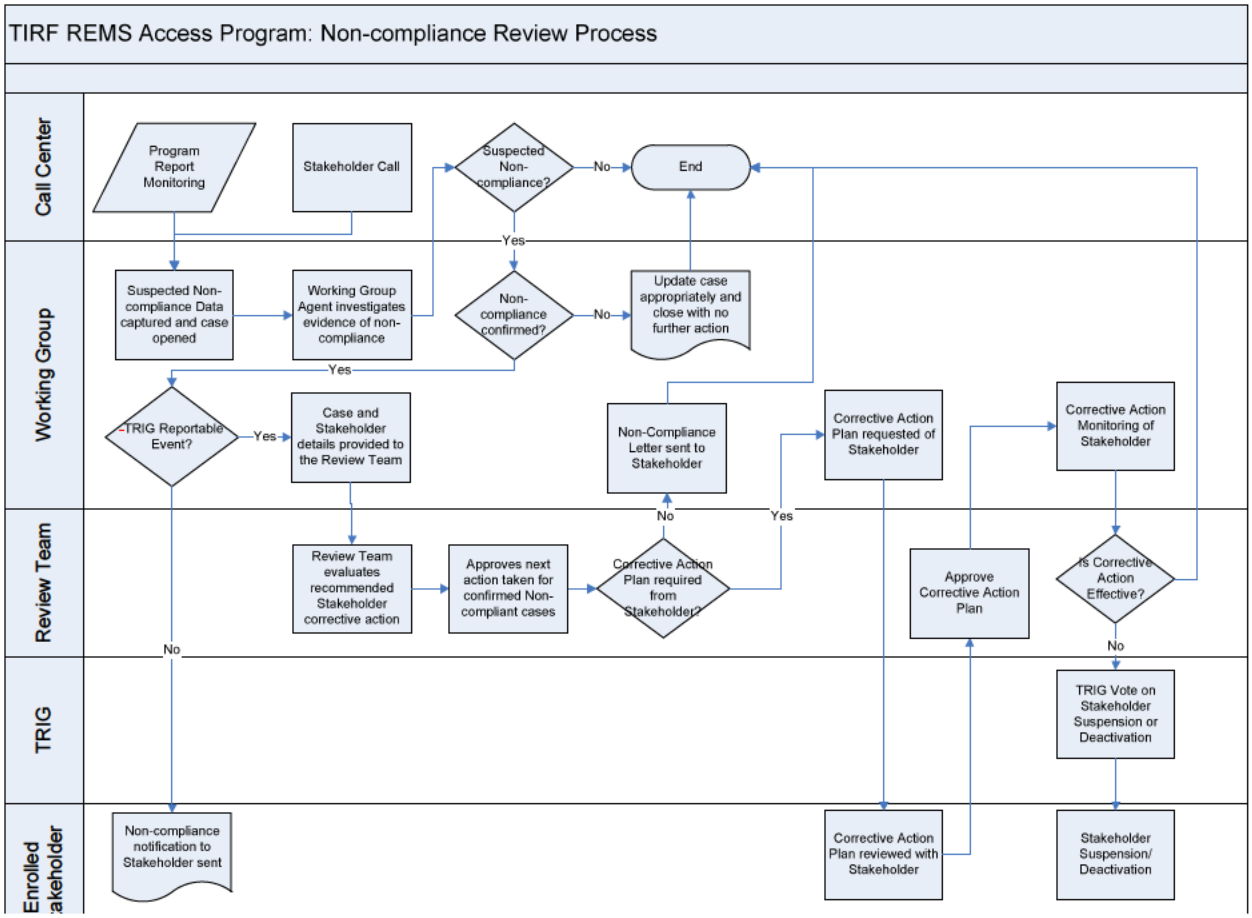
Detailed business rules will outline the process, timeline and corrective action plan for each instance of suspected or confirmed program non-compliance identified by the Working Group. Stakeholders identified as having suspected or confirmed non-compliant events may be contacted by the Working Group via letters, phone calls or fax to resolve issues related to the identified program deviation all in accordance with such business rules.

The Working Group will provide the Review Team with reports in advance of their regularly scheduled meetings and will be available to address any questions or clarifications on the content of the report. The Working Group will provide a summary of the suspected or confirmed non-compliant events that they identified during the review period.

Once the Review Team receives the report, their responsibility will be to:

- Attend all regularly scheduled Review Team meetings to review, assess and make decisions on any non-compliance issues needing attention including any issue that the Working Group could not handle because it was beyond the scope of the business rules used by the Working Group.
- Identify if an audit of a stakeholder is required
- Determine if any report or communication should be made to the FDA outside of regular TIRF REMS assessment reports.
- Determine if changes to the business rules and/or this protocol need to be made, and make such changes.

The following process flow outlines the suggested interactions between the Working Group, the Review Team and the program stakeholders as necessary monitor, review and act upon suggested corrective actions for non-compliant scenarios identified.



Identification and Investigation Process of Non-Compliant Events

Identification Process

Call center staff in the TIRF REMS Access program or TRIG sponsor companies will refer cases of potential non-compliance to the Working Group.

Investigation Process

If an instance of potential non-compliance is identified, further investigation will be conducted. This may include:

- Review case details to determine if evidence of non-compliance exists
- Make attempt(s) to contact relevant stakeholder to validate data/information and solicit further information
- Conduct further investigation of TIRF REMS Access program databases

For instances of potential non-compliance that are not described in Section 5, a suggested course of action will be presented to the Review Team. The Working Group will consult with the Review Team if proprietary or commercially sensitive information arises that would not ordinarily be shared among TRIG representatives.

4. CORRECTIVE ACTIONS FOR INSTANCES OF NON-COMPLIANCE

Corrective actions resulting from non-compliance will be determined according to the severity of the action. The stakeholders in this non-compliance protocol include prescribers, patients, distributors, and pharmacies. The primary elements for corrective action include; warnings, suspension, and deactivation based on the requirements of the TIRF REMS Access program. If a prescriber, pharmacy or distributor is suspended or deactivated, information will be made available through the program to assist unaffected stakeholders in finding alternative access to product.

Each non-compliant event will be categorized based on the level of severity of the event. The event classifications are as follows:

Minor

A minor event is defined as a first-time event within an enrollment period. An investigation will be conducted by program staff to identify the root cause of the event. Program staff will also work with the stakeholder to create and implement a corrective plan of action. The corrective plan of action must be received within 15 business days. It must be deemed acceptable and implemented within 90 days of receipt or the stakeholder will be suspended. Once the corrective

plan of action is implemented, the stakeholder will be monitored for compliance with the plan of action, and provided with a written warning for their files.

Moderate

A moderate event is defined as repeated event or a series of different [or distinct] events within the same enrollment period. An investigation will be conducted by program staff to identify the root cause of the event. This level of offense will result in a suspension from the program and possible deactivation. Program staff will work with the stakeholder to create and implement a corrective plan of action. The corrective plan of action must be received within 10 business days. It must be deemed acceptable and implemented within 90 days of receipt or the stakeholder will be deactivated. Once the corrective plan of action is implemented, the enrollment will be reinstated and the stakeholder will be monitored for compliance with the plan of action.

Serious

A serious event is defined as an event that results in serious or significant injury or potential risk to a patient irrespective of the number of previous non-compliance occurrences, or continued non-compliant events after retraining has occurred and within the same enrollment period. This level of offense will result in a deactivation from the program for a two-year period. During the two-year period, deactivated prescribers will not be able to participate in the TIRF REMS Access program for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. Following the two-year period, the stakeholder can reinstate their enrollment in the TIRF REMS Access program by going through the enrollment process.

A stakeholder may request that the result of any investigation into non-compliance be reconsidered. Only verifiable, additional information or extenuating circumstances will be considered as grounds to reinstate enrollment. Requests for reinstatement must be in writing and will be evaluated by the Review Team for final determination.

Detailed business rules will outline the process, timeline and corrective action plan for each level of program non-compliance.

The Review Groups will determine whether a suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy or distributor is part of a larger entity, the parent entity will be notified of the noncompliant activity and resultant suspension.

Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

5. EVALUATION PROCESS

5.1. INDEX OF NON-COMPLIANCE SCENARIOS

Stakeholder	Scenario		Monitoring
	#	Non-Compliance Activity	Tool
Pharmacy	1	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF pharmacy management system that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Audit or Spontaneous event reported
	2	Dispensing activity for enrolled outpatient pharmacies during reporting period not matching distributor shipment data for that pharmacy.	Audit or Sponsor reported
	3	Pharmacy is dispensing TIRF medicine while suspended or deactivated from the TIRF REMS Access program.	Audit or Spontaneous event reported
	4	Pharmacy no longer has a valid DEA	Audit or Spontaneous event reported
	5	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS Access program.	Audit or Spontaneous event reported
	6	Inpatient Pharmacy dispenses for outpatient use	Audit or Spontaneous event reported
	7	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)	Audit or Spontaneous event reported
	8	Pharmacy sold, loaned or transferred TIRF medicine inventory to another pharmacy, institution, distributor or prescriber.	Audit or spontaneous event reported
Wholesaler/ Distributor	1	Wholesaler/Distributor is suspended or deactivated from the TIRF REMS Access program and is purchasing or distributing TIRF medicines.	Sponsor reported
	2	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.	Audit or Spontaneous event reported
Prescriber	1	Prescriber is prescribing TIRF medicines while suspended or deactivated from the TIRF REMS Access program.	Audit or Spontaneous event reported
	2	Prescriber failure to have a complete PPAF on file in a timely manner (1 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date).	Program Report
	3	Prescriber no longer has a valid, schedule II DEA.	Audit or Spontaneous event reported
	4	Prescribed TIRF medicines to an opioid non-tolerant individual.	Audit or Spontaneous event

Stakeholder	Scenario		Monitoring
	#	Non-Compliance Activity	Tool
			reported
Prescriber	5	Inappropriate conversions between TIRF products.	Audit or Spontaneous event reported
Closed System Pharmacy	1	Dispensing prescriptions outside of the closed system authorization process.	Program Report
Patient	1	The Patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction	Audit or Spontaneous event reported
All Stakeholders	1	ENROLLMENT MONITORING ONLY: Monitor stakeholders who are not enrolled in TIRF and are associated with non-compliance cases.	Program Reports

5.2. REFERENCE – SEVERITY

Severity Guideline	
Level of Severity	**Definition**
Minor	The first identification of a non-compliant event within the two-year enrollment period
Moderate	Two unique non-compliance events within the two-year enrollment period
Serious	Three or more unique non-compliance events within the two-year enrollment period or an event that results in serious or significant injury or potential risk to a patient irrespective of the number of previous non-compliance occurrences

5.3. REFERENCE – CORRECTIVE ACTION

Corrective Action Guideline	
Action	**Measure**
Warning	Minor violation that demonstrates a misunderstanding of the program requirements
	Warnings are intended to re-educate stakeholders
	Patient warnings will be sent to a patient's prescriber
Suspension	Temporary deactivation from the program
	A suspended pharmacy or distributor may keep existing TIRF inventory but may not purchase or acquire additional TIRF medicines
	Pharmacies may not dispense TIRF medicines from existing inventory and distributors may not sell/distribute TIRF medicines during suspension
	If the pharmacy or distributor is part of a larger entity that entity will be notified of the suspension
	Second offense of a non-compliance event
Deactivation	Deactivations may result in multiple failures to comply with the program elements and/or non-compliance where there is no feasible corrective action
	Bars stakeholder to provide TIRF medicines as a therapy for their patients
	Pharmacies and distributors must return all existing TIRF medicine
	Patient deactivation will be sent to a patient's prescriber. Patients may only be reinstated into the program by a request from their prescriber
	Third offense of a non-compliance event

5.4. REFERENCE – MONITORING FREQUENCY GUIDELINES

Monitoring Frequency Guideline	
Report Category	**Frequency**
Existing Reports	Bi-Monthly
Report Does Not Exist	Cost/Timeline TBD - Report request will be handled via the Change Management Process
Sponsor Reported	During every Non-Compliance Review Team Meeting and as needed
KAB Surveys	12 and 24 months from the date of the REMS approval and as needed thereafter
Escalation Log	During every Quality Management Workstream meeting and as needed

6. NON-COMPLIANCE ASSESSMENT REPORTING

Confirmed non-compliance events will be provided to the Companies' 3rd party vendor for inclusion in FDA assessment reports.