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December 28, 2015

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

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Assessment
eCTD Sequence Number: 0019

Dear Drug Master File Staff:

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

Included in this submission, please find the REMS Assessment 5 at 4 years.

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

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

If you have any questions or concerns, please do not hesitate to contact Jann Kochel, U.S. Agent for McKesson, at 610-407-1738 or alternatively via email at jann.a.kochel@accenture.com.

Sincerely,

Jann A. Kochel, U.S. Agent
Accenture, LLP

Attachments: Table of Contents for the submission
Electronic Submission Specifications

Assessment – 4 Years

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments Administrative Information Page
1.16 – Risk Management Plans	REMS History REMS Assessment – 4 Years

Electronic Submission Specifications

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

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

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
Virus Definition Date	12/21/2015 rev. 2
Submission Size	Approx. 15 MB

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

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Modification No.	Date Approved	Documents Affected	Overview of Modification
1	June 5, 2012	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient Provider Agreement Form • Patient and Caregiver Overview • Dear Healthcare Provider Letter • Outpatient Pharmacy Overview • Chain Pharmacy Overview • Inpatient Pharmacy Overview • Outpatient Pharmacy Enrollment Form • Chain Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Outpatient Pharmacy Letter • Inpatient Pharmacy Letter • Dear Distributor Letter • Distributor Enrollment Form • Supporting Document	**Sequence 0002**: Edits to Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form*, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray) and minor editorial changes. *The Closed System Pharmacy Enrollment Form was not formally submitted through the Gateway but was submitted via email on May 18, 2012 and included in the June 5, 2012 FDA approval letter.
N/A	N/A	Assessment Report 1 at 6 months – due 06/28/2012	**Sequence 0003**: Assessment report covering 12/28/2011 to 04/27/2012

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

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Patient Provider Agreement Form • Chain Outpatient Pharmacy Overview • Independent Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Patient and Caregiver Overview • Prescriber Overview • Education Program • Knowledge Assessment • Frequently Asked Questions (FAQ) • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Healthcare Provide Letter • Dear Distributor Letter • REMS • Supporting Document • Website Landing Page	TIRF REMS Access Program
N/A	N/A	Assessment Report 3 at 2 years – due 12/28/2013	**Sequence 0007: Assessment report covering 10/29/2012 to 10/28/2013**

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Safety Surveillance Report #1 – due 03/31/2014	**Sequence 0008:** **Safety surveillance data covering Q4 2012 to Q3 2013**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ	**Sequence 0009**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the currently approved TIRF products list on the FDA Approved REMS website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Supporting Document • Website Prototype	• FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed
N/A	N/A	Cash Claim Information Request Response – due 05/30/2014	**Sequence 0010: Response to 5/16/2014 FDA Cash Claim Information Request**
N/A	N/A	DMF Annual Report – due 08/20/2014	**Sequence 0011: DMF Annual Report**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Knowledge Assessment • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy	**Sequence 0012**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the TIRF Products webpage on the TIRF REMS Access website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ • Supporting Document • Website Prototype	appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed • Updated Education Program and Knowledge Assessment to incorporate approved labeling supplement
3	December 24, 2014	Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter	**Sequence 0013**: Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter
N/A	N/A	Assessment Report 4 at 3 years – due 12/28/2014	**Sequence 00014: Assessment report covering 10/29/2013 to 10/28/2014**

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	BioDelivery Sciences International – Letter of Authorization	**Sequence 0015: BioDelivery Sciences International – Letter of Authorization**
N/A	N/A	Actavis Laboratories Inc. – Letter of Authorization	**Sequence 0016: Actavis Laboratories Inc. – Letter of Authorization**
N/A	N/A	DMF Annual Report – due 08/20/2015	**Sequence 0017: DMF Annual Report**
N/A	N/A	36-Month Assessment – Consolidated Information Requests	**Sequence 0018: Response to FDA 36-Month Assessment Information Requests**
N/A	N/A	Assessment Report 5 at 4 years – due 12/28/2015	**Sequence 00019: Assessment report covering 10/29/2014 to 10/28/2015**

Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program 48-month Assessment Report
Reporting Timeframe:	29 OCT 2014 to 28 OCT 2015
Document Number:	FINAL v 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.

Confidentiality Statement

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LIST OF ABBREVIATIONS

AAPCC	American Association of Poison Control Center
ANDA	Abbreviated New Drug Application
AP	Authorized Pharmacist
BTP	Breakthrough Pain
CS	College Survey
CAP	Corrective Action Plan
CFR	Code of Federal Regulations
CSR	Call Center Service Representative
DMF	Drug Master File
DoD	Department of Defense
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Provider
ID	Identification
IR	Immediate Release
KAB	Knowledge, Attitude, and Behavior
LTC	Long-Term Care
MedDRA	Medical Dictionary for Drug Regulatory Activities
MLU	Military Logistics Unit
NCPDP	National Council for Prescription Drug Program
NCRT	Non-Compliance Review Team
NDA	New Drug Application
NDC	National Drug Code
NPI	National Provider Identifier
OTP	Opioid Treatment Program
PMS	Pharmacy Management System
PPAF	Patient-Prescriber Agreement Form
PT	Preferred Terms
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
SKIP	Survey of Key Informants' Patients
SOP	Standard Operating Procedure
TC	Treatment Center
TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl product(s)
TIRF REMS Access	REMS program for TIRF medicines
TIRF Sponsors	The group of sponsors that are submitting this REMS
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
VA	Veteran's Association

OVERVIEW

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

In the last 3 years, the TIRF REMS Access program assessment reports were submitted according to the following schedule:

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

This fifth REMS assessment report (48 months) covers the timeframe from October 2014 to 28 October 2015. As per agreement with FDA, safety surveillance analyses necessitated slightly different time periods as noted in the relevant sections within the report.

As of 12 March 2015, the TIRF REMS Access program has been fully implemented for 3 years.

Prescriber Enrollment

At the end of this reporting period, 9,096 prescribers were enrolled in the TIRF REMS Access program. A total of 2,340 were newly enrolled in the TIRF REMS Access program and 1,822 prescribers successfully re-enrolled during the reporting period. A total of 2,095 prescribers were inactivated, with 2,071 (98.9%) due to expiration of their enrollment at some time during the reporting period. A few prescribers were inactivated because they opted out of the program or were deceased. Based on historical review of the prescription activity by the subsequently inactivated prescribers, access to TIRF medicines appears unimpeded.

During this reporting period, 53 prescribers attempted enrollment but were still pending 3 to 6 months after initiating the enrollment process and 309 prescribers were pending enrollment for longer than 6 months since initiating the enrollment process. The most common reasons for pending enrollment were: no attestation, training not complete, and knowledge assessment failure on the first attempt.

Pharmacy Enrollment

At the end of this reporting period, 43,216 pharmacies were enrolled (had activity in this reporting period or remained enrolled from the previous reporting period) in the TIRF REMS Access program. A total of 5,892 pharmacies were newly enrolled in the TIRF REMS Access program during this reporting period. Of the newly enrolled dispensing pharmacies (e.g., excluding pharmacy headquarters), 5,286 were chain pharmacy stores, 510 were independent outpatient pharmacies, 87 were inpatient pharmacies, and 7 were closed system pharmacy locations. During this reporting period, a total of 4,920 pharmacies were inactivated, with 4,810 inactivations due to expiration of their enrollment. Based on review of the inactivated pharmacies historical dispensing volume, access to TIRF medicines appears unimpeded.

A total of 44 pharmacies attempted enrollment but were still pending 3 to 6 months after initiating the process and a total of 198 pharmacies were pending enrollment for longer than 6 months. The most common reasons for pending enrollment were pending test transaction verification, no attestation, and training not complete.

Distributors Enrollment

During the reporting period, there were 3 newly enrolled distributors and 13 distributors that re-enrolled. There were 3 distributors inactivated during the reporting period due to enrollment expiration; 1 of these distributors had re-enrolled by the end of the reporting period. Although there were 2 distributors who remained inactivated at the end of the reporting period, access to TIRF medicines is unimpeded because both locations were acquired by other entities.

Patients

As of the end of the reporting period 37,930 patients have been enrolled, of these 8,740 were newly enrolled in the TIRF REMS Access program during this reporting period. Because patients are passively enrolled with their first prescription, they are not required to re-enroll at any point. Instead, prescribers must renew a patient's Patient-Prescriber Agreement Form (PPAF) every 2 years. By the design of the program, a patient's enrollment status will never change to inactivated.

Dispensing Activity

A total of 152,686 prescriptions were submitted to the TIRF REMS Access program for approval in the current reporting period, including 152,228 prescriptions from non-closed system pharmacies and 458 prescriptions from closed system pharmacies. Of the total prescriptions submitted for approval, 143,763 (94.2%) were approved for dispensing without encountering any REMS-related rejections. A total of 8,923 prescriptions encountered at least one REMS-related rejection due to failure to meet REMS requirements for the prescriber and/or patient and/or pharmacy. Of these, 1,735 prescriptions were ultimately authorized for dispensing and the remaining 7,188 prescriptions were never authorized for dispensing. A single prescription may have been submitted and rejected multiple times.

The average time for a prescription that had at least one REMS-related rejection to become authorized was 6.7 days (median 1.3 days).

Non-Compliance

During the current reporting period, 101 confirmed instances of stakeholder non-compliance with the TIRF REMS Access program requirements were reviewed and investigated. This included 89 prescriber reports and 12 non-closed system pharmacy reports. There were no wholesaler/distributor or closed system pharmacy reports. A description of these cases including 94 activity reports and 7 narratives are included in Section 6, Table 22 and Table 23, respectively.

Closed System Pharmacy and Inpatient Pharmacy Audits

Audits of 6 closed system pharmacy entities were conducted during this reporting period. Two closed system entities (#361 and #376) 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 Non-Compliance Review Team (NCRT). Both non-compliance cases have since been closed. A description of the audits and details of these cases and actions taken are provided in Section 6.2.1.

Since submission of the 36-Month FDA Assessment Report, the TIRF REMS Industry Group (TRIG) developed and implemented an inpatient pharmacy questionnaire to conduct the required inpatient pharmacy audits. Audits of 6 inpatient pharmacies were conducted during this reporting period and no non-compliance was identified for any inpatient pharmacy. A description of the audit questionnaire and a summary of the audit findings are included in Section 6.2.2.

Safety Surveillance Data

Safety surveillance data for this 48-month assessment report consists of data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System and aggregate adverse event data from all TRIG sponsors.

RADARS System Data

Data from 5 RADARS System Programs that gather data from unique populations along the spectrum of drug abuse were used to monitor for the non-medical use (abuse and misuse) of TIRF products. Based on FDA request, the data included in this report compare event rates for a time period prior to full implementation of the TIRF REMS and a time period after REMS implementation.

(b) (4)

A description of these data is included in Section 7.4 of this report, and the complete methods and results are included in the RADARS System Report in Appendix 12.6.

Aggregate Spontaneous Adverse Event Data of Interest

Spontaneous adverse event data of interest including events of addiction, overdose, death and pediatric exposures were provided by each sponsor and aggregated into one comprehensive line listing. A total of 312 unique case reports were identified as meeting the criteria for inclusion in the analysis based on case preferred terms and review of the case narrative information. Of the 312 cases, the highest proportion of reports had an outcome of death (291, 93.3%), and many reports had no cause of death provided. There were 12 (3.8%) reports of addiction, and 4 (1.3%) pediatric exposures. There were 6 (1.9%) reported overdoses to an identified TIRF product.

After a review of the associated MedWatch Forms or narratives for root cause analysis, no reports of inappropriate conversions between TIRF products were noted. Additionally, none of the narratives indicated unintentional exposures or use by non-opioid tolerant patients. There was one report of accidental exposure with an outcome of recovered/resolved during the reporting period. There were 4 reports of pediatric exposure. In 3 of the 4 reports, the medication was intentionally prescribed to the pediatric patient. The fourth report had insufficient information to determine if the pediatric patient took the TIRF medicine.

When comparing the current reporting period (29 August 2014-28 August 2015) rate of adverse events by prescription to results in the 36-month report (29 August 2013-28 August 2014), the number of cases per 100,000 prescriptions increased for addiction (10.7 vs. 4.2), overdose (5.3 vs. 0), and pediatric exposure (3.6 vs. 2.1). Conversely, the number of cases of death per 100,000 prescriptions decreased in the current reporting period compared with the 36-month report period (258.6 vs. 383.2).

When comparing the current reporting period (29 August 2014-28 August 2015) rate of adverse events by patient to results in the 36-month report (29 August 2013-28 August 2014), the number of cases per 100,000 patients increased for addiction (75.4 vs. 27.1), overdose (37.7 vs. 0), and pediatric exposure (25.1 vs. 13.5). Conversely, the number of cases of death per 100,000 patients decreased in the current reporting period compared with the 36-month report period (1827.7 vs. 2450.6).

Additional details are included in Section 7.2.

Knowledge, Attitudes, and Behavior (KAB) Surveys

TRIG determined that a desired threshold of 65% or greater would be considered to represent adequate understanding of each concept or key risk message for the 48-month KAB surveys. The purpose of establishing this threshold was to assist TRIG in tracking and monitoring the level of understanding of key risk messages across each wave to determine if the goals of the REMS are being met and if any modification to the REMS is required.

Patient Survey Results

In the 48-month patient survey, 13 of the 19 components of the 6 key risk messages had a response rate >80%, and 3 components had a correct response rate between 67.7% and 74.8%.

The remaining 3 components within key risk messages 2 and 3 had a correct response rate which fell below the desired threshold of 65%. Patients scored consistently low on 2 of 19 components across all survey waves which included 1) TIRF medicines should not be taken for long-lasting pain not from cancer, like arthritis joint pain (43.9% correct), and 2) a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (39.4% correct). In addition, revising one question (TIRF medicines should only be taken by patients who are opioid tolerant) to be specific to 'cancer' patients, resulted in a large decrease in the correct response rate from the previous survey (85.2% to 43.5%), which may indicate that some respondents were receiving TIRF medicine for a non-cancer associated indications.

The consistently high level of patient understanding of key risk messages in this 48-month survey indicates that the goals of the TIRF REMS are being met with existing tools. In general, there is an overall trend across all patient/caregiver KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward maintenance or improvement in patient/caregiver knowledge and understanding of the key risk messages.

Pharmacist Survey Results

In the 48-month pharmacist survey, 20 of the 29 components of the 4 key risk messages had a response rate >80%, and 7 components had a response rate between 65.1% to 78.7%. Two components within the key risk messages had a correct response rate below the desired threshold of 65% (Component 6c and Component 9e). The correct response rate for Component 6c (A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine) was 41.9%. This component was added to the 48-month survey based on feedback provided by FDA in the 24-month and the 36-month FDA REMS Acknowledgement Letter. Correct response rate for Component 9e (Chronic non-cancer pain is not an indication for which TIRF medicines can be prescribed) was 50.8% for this 48-month survey. Component 9e has had a low correct response rate across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). The survey score for Component 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

The consistently high level of pharmacists' understanding of key risk messages in the latest (48-month) survey indicates that the Education Program for Pharmacists is meeting the goals of the TIRF REMS. In general, there is an overall trend across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in pharmacist knowledge and understanding of the key risk messages.

Prescriber Survey Results

In the 48-month prescriber survey, 21 of the 31 components of the 4 key risk messages had a correct response rate >80% and 9 components had a correct response rate between 67.7% and 78.7%. For Component 9e, 201 prescribers (64.8%) indicated they do not prescribe TIRF medicines for chronic non-cancer pain. The 34.2% of prescribers who stated they do prescribe TIRF medicines for chronic non-cancer pain were presented with 2 additional questions as

requested by the FDA; the type of chronic pain conditions they prescribe a TIRF medicine to treat, and the reasons for selecting a TIRF medicine to treat these conditions. Based on prescriber responses, and the high percentage of respondents who indicated they received and read the REMS educational materials, the responses may reflect behavior more than knowledge. That is, prescribers are aware of the labeled indication but choose to prescribe off-label for certain patients.

The consistently high level of prescriber understanding of key risk messages in the latest (48-month) survey indicates that the Education Program for Prescribers is meeting the goals of the TIRF REMS. In general, there is an overall trend across all prescriber KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in prescriber knowledge and understanding of the key risk messages.

1 BACKGROUND

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

Opioids are formulated as both extended-release and immediate-release (IR) products. Extended- release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' chronic pain control (breakthrough pain, BTP). All the TIRF medicines are short-acting fentanyl products.

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

The FDA has determined that a REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The group of Sponsors who are submitting this 48-month REMS (Actavis Laboratories FL, Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Galena Biopharma, Inc., Insys Therapeutics Inc., Mallinckrodt Pharmaceuticals, Mylan, Inc. and Par Pharmaceutical, Inc.) are herein referred to as TIRF Sponsors. Two companies joined the TRIG during the reporting period: Actavis Laboratories FL, Inc. joined on 06 February 2015 and BDSI replaced Meda Pharmaceuticals on 11 March 2015. The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. This report has been prepared by United BioSource Corporation (UBC).

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

Table 1 TIRF Medicines

Product Name (active ingredient)/formulation
NDA 22510, ABSTRAL (fentanyl) sublingual tablets
NDA 20747, ACTIQ (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 21947, FENTORA (fentanyl buccal tablet)
NDA 22569, LAZANDA (fentanyl) nasal spray
NDA 22266, ONSOLIS (fentanyl), buccal soluble film
NDA 202788, SUBSYS (fentanyl sublingual spray)
ANDA 77312, fentanyl citrate oral transmucosal lozenge
ANDA 78907, fentanyl citrate oral transmucosal lozenge

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

The initial REMS was approved on 28 December 2011 and went live on 12 March 2012. The FDA required 6-month and 12-month reports during the first year after approval, and then annually thereafter (Table 2). Reporting periods for each assessment report are described below. Data cut-off is 60 days prior to the submission date. Due to availability of data and the time needed to generate/analyze the data, safety surveillance reporting utilizes a modified data cut-off. The RADARS System reporting includes data from 3rd quarter 2012 through 2nd quarter 2015 and the aggregate spontaneous adverse event data of interest includes data from 29 August 2014 through 28 August 2015.

Table 2 Assessment Report Periods

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

2 REMS GOALS

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.

3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors are executing the TIRF REMS Access program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access program, including patients, prescribers, pharmacies and distributors, must be enrolled

in the TIRF REMS Access program, educated on the requirements of the program and required to document that they understand and will abide by the ETASU.

Program materials are provided on the TIRF medicines in addition to product-specific materials. The Education Program and Knowledge Assessment components of the program contain both TIRF medicine class and product-specific components. All program tools, including enrollment forms, PPAFs, stakeholder letters, and overview documents containing program information specific to the TIRF REMS Access program, are available at www.TIRFREMSACCESS.com.

The program procedures are monitored for adherence and the TIRF Sponsors will continue to conduct ongoing and retrospective analyses as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

3.1 Additional Elements

3.1.1 Medication Guide

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

3.1.2 Letters to Healthcare Professionals

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

3.2 Elements to Assure Safe Use

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

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

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to review the TIRF REMS Access Education program, successfully complete the Knowledge Assessment and submit a completed and signed TIRF REMS Access program enrollment form. The authorized pharmacist ensures that their Pharmacy Management System (PMS) is able to support communication with the TIRF REMS Access program using established telecommunication standards. This requires submitting standardized test transactions to validate the system enhancements. The authorized pharmacist is responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program.

For chain pharmacies, an authorized chain pharmacy representative completes the enrollment process on behalf of all individual store locations associated with that chain. The authorized chain pharmacy representative acknowledges that training has been provided to all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education program and Knowledge Assessment have been completed, the authorized chain pharmacy representative, on behalf of the chain, is required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form.

For inpatient pharmacy enrollment, the authorized pharmacist is required to review the TIRF REMS Access Education program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist is required to acknowledge that they understand that outpatient pharmacies within their facility must be enrolled separately.

Implementation of the TIRF REMS Access program for closed system outpatient pharmacies launched on 30 June 2012. Closed system outpatient pharmacies are integrated healthcare systems that dispense for outpatient use but their PMS is unable to support the process of electronically transmitting the validation and claim information. To enroll in the TIRF REMS Access program, the authorized pharmacist must review the TIRF REMS Access Education program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. A list of closed system pharmacy locations that have been trained must be provided to the TIRF REMS Access program.

Patients are passively enrolled in the TIRF REMS Access program when their first prescription is processed by a 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 3 prescriptions are allowed within 10 working days from the date that the patient has their first prescription filled. No further prescriptions are to be dispensed after the 10 working day window until a completed PPAF is received. A patient's HCP can submit a copy of the PPAF to the TIRF REMS Access program via the Web site, fax, or United States (US) mail.

3.2.1 Prescription Verification

Following initial patient enrollment, upon processing of a patient's first TIRF medicine prescription, pharmacies 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. Prescription verification is not required for inpatient use of TIRF medicines.

Non-Closed System Pharmacies

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

Upon receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the prescription details are entered into their PMS and a transaction is sent to the TIRF REMS Access program via a switch provider. If the patient is not enrolled and this is their first prescription, the TIRF REMS Access program uses the transaction data to automatically transfer patient details into the TIRF REMS Access program database for passive enrollment.

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

In the case where a prescription passes all REMS edits, a billing request is then sent to the payer by the switch provider. Once the payer authorizes payment, the switch provider then authorizes the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which is captured by the TIRF REMS Access program.

Specific reasons why a prescription would not meet a REMS edit are described in Table 17.

If the prescription does not pass all REMS edits (e.g., one of the stakeholders was not enrolled), the TIRF REMS Access program rejects the claim prior to the claim being forwarded to the payer and the pharmacy receives a rejection notice from the switch provider. This automated feedback indicates the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notifies the pharmacist to contact the TIRF REMS Access program Call Center for further information.

Closed System Outpatient Pharmacies

Upon receipt of a prescription for a TIRF medicine at an enrolled closed system outpatient pharmacy, a pharmacy staff member will contact the TIRF REMS Access program via phone or fax to provide prescription details for verification. The TIRF REMS Access program then validates the enrollment status for the patient, prescriber and pharmacy. If the patient is not enrolled, the TIRF REMS Access program will use this transaction information to automatically transfer patient details into the TIRF REMS Access database for passive enrollment. If all three stakeholders are enrolled (i.e., passes all REMS edits), the closed system outpatient pharmacy is given an authorization number which is captured by the TIRF REMS Access program. If the prescription does not pass all REMS edits (e.g., one of the stakeholders is not enrolled), the TIRF REMS Access program will not provide an authorization number and the closed system

outpatient pharmacy will receive a rejection notice. This feedback is provided to the closed system outpatient pharmacy via phone or fax and includes the reason for rejection, information on how the rejection may be resolved and instructions to not dispense the TIRF prescription until resolution is reached.

3.3 Implementation System

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

3.3.1 Wholesaler/Distribution Enrollment and Fulfillment

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

For the purpose of the TIRF REMS Access program, the term distributor refers to a wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors received a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies upon FDA approval of the program. To enroll, the distributor's authorized representative must review the distributor program materials, complete and sign the Distributor Enrollment Form and fax it to the TIRF REMS Access program. TIRF Sponsors have processes in place to prevent shipping TIRF medicines to any distributor who has not completed and signed the enrollment form.

3.3.2 The TIRF REMS Access Program Compliance [Metric 22]

The TIRF REMS Access program NCRT was created by the TRIG on 19 October 2012 and is tasked with reviewing reports of suspected non-compliance with the TIRF REMS Access program requirements. The NCRT is composed of membership from all TRIG sponsors. There are currently 24 individuals across the 9 sponsors; the functional areas or specialties represented by the members include Regulatory, Medical Affairs, REMS Specialist, Legal, Quality and Drug Safety.

TIRF Sponsors monitor prescriber, pharmacy, and wholesaler/distributor activities for compliance with TIRF REMS Access program requirements. Corrective actions (e.g., re-education, additional monitoring, process revision, and stakeholder inactivation) are instituted by the TIRF Sponsors as appropriate if non-compliance is confirmed. The Non-Compliance Plan is described in Section 4.1.4 (Metric 22) and results of non-compliance investigations are included in Section 6 of this report. The full Non-Compliance Protocol is included in Appendix 12.1.

3.3.3 TIRF REMS Access Program Call Center

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

4 REMS ASSESSMENT PLAN METHODS

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

The 36-Month FDA assessment report Acknowledgement Letter included multiple new requests to be incorporated into the 48-Month FDA assessment report. Due to timing of this correspondence, requested items #2 and #3 (Table 3) are not included in this assessment report. As communicated to FDA on 08 September 2015, these items will be reported in the 48-Month Supplemental Report estimated to be submitted to FDA on 04 May 2016.

In reference to request #4, TRIG has provided information in Section 5.1.2 to address the potential patient-access issues of health professionals and pharmacies who did not re-enroll in the TIRF REMS Access program. Based on review of their historical prescription activity, only 8.6% of prescribers had recent prescription activity and chose not to re-enroll. These prescribers account for less than 6.0% of the cumulative number of prescribers who have ever been inactivated and these prescribers had an average of no more than 4 prescriptions total over the course of the reporting period. At present 1,144 pharmacies remained inactivated at the end of this reporting period with 64% never having had any TIRF prescription activity since their initial enrollment in the TIRF REMS Access program. Based on this analysis, there is no barrier to patient access and further outreach is unwarranted.

Table 3 36-Month FDA Assessment Report FDA Acknowledgement Letter Requests

Request Number*	FDA Request
2.	In order to assess the TIRF REMS goal of prescribing and dispensing TIRF products only to appropriate patients, which includes use only in opioid-tolerant patients, conduct the following analysis: Identify a health care database that includes an adequate number of TIRF product users. Within that database, by year, provide the number of total unique patients dispensed an initial prescription for a TIRF product in the outpatient setting. Determine what proportion of those total unique patients received a prescription for an opioid analgesic product prior to the prescription for the TIRF product. Provide these data separately for patients receiving an opioid analgesic within the 7-days prior and within the 30-days prior to the initial TIRF prescription. Before embarking on this analysis, provide to FDA your choice of database and the estimated number of TIRF users in the database so that we can determine if the number is adequate.
3.	We are not able to establish whether the TIRF REMS is achieving the goal of preventing inappropriate conversion between TIRF medicines. In order to better understand how many people are at risk for inappropriate conversion between TIRF medicines, we need a better idea of how long patients stay on one TIRF and whether they shift between TIRF products or just stop them completely. Conduct a persistency analysis based on the data available on the prescriptions processed through the switch system used by retail pharmacies. This analysis should demonstrate the number of patients starting on a TIRF and follow them over weeks and months to summarize their treatment course and change in therapy. The TIRF products can be grouped together, and the specific drug does

Request Number*	FDA Request
	not need to be disclosed. Following the discontinuation of the TIRF, the persistency analysis should also depict what treatment option the patient uses next. This will be either full discontinuation or switching to another TIRF product. There may be gaps in between prescriptions; 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.
4.	Conduct outreach to a representative sample of those health professionals and pharmacies that did not re-enroll in the TIRF REMS Access program so as to ascertain their reasons and report the results in your next assessment report. We are concerned about potential patient access issues.

*Numbering is aligned with the numbering of the FDA requests communicated in the 36-Month FDA assessment report Acknowledgement Letter.

4.1 Data Sources for REMS Assessments

Data were collected from the following main sources as described in detail below: a) TIRF REMS Access program utilization statistics (Section 4.1.1), b) dispensing activity for enrolled pharmacies (Section 4.1.2), c) program infrastructure and performance, d) TIRF REMS Access non-compliance plan, e) safety surveillance, and f) periodic surveys of patients, HCPs, and pharmacies. All programmed source tables and figures, as well as source data are on file at UBC and available upon request. The individual metrics for each main data source are provided below with a direct link to the results sections of the report.

Note: Every metric number shown in the following tables is used to identify the respective metric in the headers and text of the results (see Section 5).

4.1.1 The TIRF REMS Access Program and Product Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and distributors, the following metrics were tabulated for the current reporting period and cumulatively.

Metric Number*	Metric
a.	**Patient Enrollment**
1.	Number of unique patients enrolled
2.	Number of patients inactivated
b.	**Prescriber Enrollment**
3.	Number of prescribers enrolled
4.	Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending
5.	Number of prescribers inactivated

Metric Number*	Metric
c.	**Pharmacy Enrollment**
6	Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities)
7.	Number of pharmacies that attempted enrollment but whose enrollment is pending >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type)
8.	Number of pharmacies inactivated by type (inpatient, chain, independent, closed system)
d.	**Distributor Enrollment**
9.	Number of distributors enrolled
10.	Number of distributors inactivated

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.2 Dispensing Activity for Enrolled Pharmacies

For the assessment of dispensing activity the following metrics were tabulated and stratified by pharmacy type for the current reporting period and cumulatively.

Metric Number*	Metric
11.	Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription/transactions per closed system entity
12.	Number of prescriptions/transactions denied/rejected and the reasons for denial/rejection. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)
13.	The mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized
14.	Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF
15.	Number of prescriptions dispensed after ten days without a PPAF in place

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.3 Program Infrastructure and Performance

The following metrics on program infrastructure performance were collected and summarized for the current reporting period.

Metric Number*	Metric
16.	Number of times a backup system was used to validate a prescription, with reason(s) for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described
17.	Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions
18.	Call center report with • Overall number of contacts • Summary of frequently asked questions • Summary of REMS-related problems reported
19.	Description of corrective actions taken to address program/system problems

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.4 TIRF REMS Access Program Non-Compliance Plan

The TIRF sponsors provide the following data regarding non-compliance in each assessment report (per reporting period).

Metric Number*	Metric
20.	Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include: • Verification of training for all pharmacists dispensing TIRF products • Numbers of prescription authorizations per closed system • 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. Data to include the 12-month period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic versus manual process). • Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

Metric Number*	Metric
21.	Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance starting in the 48-Month assessment report. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period. These reports are to include: • Verification of training for all pharmacists dispensing TIRF products • Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program • Describe any corrective actions taken for any non-compliance identified during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events
22.	Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as: • Description of how the NCRT defines a non-compliance event • Description of how non-compliance information is collected and tracked • Criteria and processes the Team uses to make decisions • Summary of decisions the Team has made during the reporting period • How the Team determines when the compliance plan should be modified
23.	Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action
24.	Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences
25.	Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences
26.	Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified
27.	Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified
28.	Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.4.1 Non-Compliance Monitoring

The goal of the Non-Compliance Plan is to help TRIG identify and investigate deviations from and non-compliance with TIRF REMS requirements to ensure patient safety and continuously improve the program. A confirmed non-compliance event is one for which the information collected through investigation of the potential non-compliance event clearly indicates that a

program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified.

The TIRF REMS Access program routinely monitors stakeholder activity to identify potential incidents of non-compliance events with program requirements and investigates all reports of suspected non-compliance. 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 are tracked through a non-compliance case that is opened on the stakeholder record 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 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 Corrective Action Plan (CAP). All CAPs are reviewed and approved by the NCRT.

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.

As requested by FDA in the 36-Month FDA Assessment Report Acknowledgement Letter, the full Non-Compliance Protocol is included in Appendix 12.1.

4.1.5 Safety Surveillance

The following safety surveillance data were collected. Reporting periods for each type of data were modified based on timing of availability of data.

Metric Number*	Metric
29.	TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 Code of Federal Regulations (CFR) 314.80 and the sponsor's respective Standard Operating Procedures
30.	TIRF Sponsors will produce one comprehensive report that presents spontaneous adverse event data from all sponsors of the TIRF REMS Access program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following: • Line listings under each category of adverse events of interest as listed above • Line listings should provide at a minimum the following information: o Identifying case number o Age and Gender of the patient o Date of the event as well as of the report o The Preferred Terms o Indication of TIRF use o Duration of TIRF therapy o Concomitant medications

Metric Number*	Metric
	○ Event Outcome • Other metrics of interest include: ○ Number of event reports in each event category of interest ○ Counts of adverse events related to inappropriate conversions between TIRF products ○ Counts of adverse events related to accidental and unintentional exposures ○ Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients • Duplicate cases are identified and eliminated • Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such • For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events • Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year
31.	Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Metric 30 directly above: • Non-medical use of prescription drugs • Surveys conducted at substance abuse treatment programs • College surveys • Poison control center data • Impaired health care workers • Drug-related hospital emergency department visits • Drug-related deaths • Other databases as relevant

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.6 Periodic Surveys of Patients, Prescribers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements are evaluated through Knowledge, Attitude, and Behavior (KAB) surveys. The surveys are administered to selected prescribers, pharmacies, and patients.

5 RESULTS

5.1 REMS Program Utilization

Described in this section are the total numbers of all enrolled stakeholders (prescribers, patients, pharmacies, and distributors), as well as stakeholder inactivations, dispensing activities, and barriers or delays in patient access.

5.1.1 Patient Enrollment [Metric 1 and 2]

During the current reporting period, there were 8,740 newly enrolled patients (Table 4). Because patients are passively enrolled with their first prescription there is no patient re-enrollment, but prescribers are required to renew PPAFs with patients every 2 years. By design, a patient's enrollment status will never change to inactivated.

Table 4 Patient Enrollment

Parameter	Current Reporting Period 29OCT2014 to 28OCT2015 Number of Newly Enrolled Patients N (%)	Cumulative[a,b] 28DEC2011 to 28OCT2015 Total Number of Enrolled Patients N (%)
Total Number of Enrolled Patients	8,740[a]	37,930[b,c]

[a] An enrolled patient is a patient who has received at least one prescription for a TIRF prescription.
[b] Includes patients that transitioned into the TIRF REMS Access program from other individual REMS programs.
[c] Cumulative patients from the end of prior period may differ from last period's report due to reconciliation of duplicate patients.

5.1.2 Prescriber Enrollment and Inactivations [Metric 3, 4, 5]

Cumulatively there have been 15,100 prescribers who have successfully completed enrollment in the program. At the end of this reporting period there are 9,096 prescribers who are currently enrolled. This includes 2,340 newly enrolled prescribers, 1,822 prescribers who re-enrolled and 4,934 who remain active from a previous period (Table 5). Table 6 shows those prescribers who have been inactivated.

Table 5 Prescriber Enrollment

Parameter	Current Reporting Period[a] 29OCT2014 to 28OCT2015 N (%)
Number of Prescribers with Enrollment Activity In This Reporting Period	4,162
Number of Newly Enrolled Prescribers	2,340 (56.2%)
Number of Re-Enrolled Prescribers	1,822 (43.8%)
Number of Prescribers Who Remain Enrolled from Previous Reporting Periods	4,934
Total Number of Prescribers Enrolled as of the End of This Reporting Period	9,096
Cumulative Number of Prescribers Ever Enrolled[b,c]	15,100

[a] Percentages are based on the total number (N) of enrolled prescribers
[b] Cumulative is defined as sum of all reporting periods.
[c] Number includes prescribers who transitioned into the TIRF REMS Access program

A total of 2,095 prescribers were inactivated at some point during the current reporting period, and the majority of these (2,071, 98.9%) were due to expiration of enrollment. It should be noted that a prescriber is required to enroll every 2 years within the TIRF REMS Access program. Of those 2,071 prescribers whose enrollment expired at some point during the current reporting period, 1,650 (79.7%) remained expired at the end of the reporting period (Table 6). In total, there were 6,007 prescribers who remained inactivated at the end of the reporting period. Of the total 6,007 prescribers inactivated as of the end of this reporting period, 8.6% (n=516) are those prescribers who had recent prescription activity and chose to not re-enroll. These prescribers account for less than 6.0% (516/8,730) of the cumulative number of prescribers who have ever been inactivated and these prescribers had an average of no more than 4 prescriptions total over the course of the reporting period.

Table 6 Prescriber Inactivations

Parameter	Current Reporting Period[a] 29OCT2014 to 28OCT2015 N (%)
Number of Prescribers Who Became Inactivated During this Reporting Period	2,095
Reason(s) For Inactivation[b]	
Deceased	6 (0.3%)
Program Opt-Out	13 (0.6%)
Non Compliant[c]	2 (0.1%)
Suspended	4 (0.2%)
Enrollment Expired[d]	2,071 (98.9%)
Enrollment remained expired at end of period	1,650 (79.7%)
Number of Prescribers Inactivated in This Time Period who Remain Inactivated as of the End of this Reporting Period	1,671
Number of Prescribers Who Were Inactivated in a Previous Reporting Period and Remain Inactive as of the End of This Reporting Period	4,336
Total Number of Prescribers Inactivated as of the End of this Reporting Period	6,007
Cumulative Number of Prescribers Who Have Ever Been Inactivated[e]	8,730

[a] Prescribers whose status is 'inactive' at least once during the reporting period.
[b] Percentages are based on the total number (N) of inactivated prescribers. A prescriber may have more than one reason for inactivation.
[c] Prescribers may be included as both "non-compliant" and "suspended" since before becoming inactivated for non-compliance, prescribers go through a suspension period.
[d] Prescribers whose status is 'Inactive-Expired' at any time during the reporting period.
[e] Cumulative is defined as sum of all reporting periods.

During the current reporting period, there were 53 prescribers who attempted enrollment but whose enrollment was pending 3 to 6 months later. A total of 309 prescribers were pending enrollment for more than 6 months within the current reporting period. Prescribers may have attempted enrollment and become pending in another reporting period.

For prescribers pending enrollment for 3 to 6 months, the most frequent reasons were no attestation (77.4%), training not complete (52.8%), and knowledge assessment failure on the first attempt (15.1%). For prescribers pending enrollment for more than 6 months, the most frequent reasons were similar and included no attestation (73.1%), training not complete (59.5%), and knowledge assessment failure on the first attempt (16.5%).

The number of prescribers that attempted enrollment but are still pending enrollment for 3 to 6 months or more than 6 months, and the reasons for pending enrollment are shown in Table 7.

Table 7 Prescribers Pending Enrollment

Parameter	Current Reporting Period[a] 29OCT2014 to 28OCT2015	
	Prescribers Pending Enrollment ≥3 – 6 Months[b]	**Prescribers Pending Enrollment >6 Months[b]**
Prescribers Who Attempted Enrollment but are Still Pending Enrollment[c]	53	309
Reasons for Pending Enrollment		
Assessment Failure - Sixth Attempt	0	1 (0.3%)
Invalid DEA	4 (7.5%)	24 (7.8%)
Invalid NPI	2 (3.8%)	14 (4.5%)
Knowledge Assessment Failure - First Attempt	8 (15.1%)	51 (16.5%)
Knowledge Assessment Failure - Second Attempt	1 (1.9%)	6 (1.9%)
Knowledge Assessment Failure - Third Attempt	1 (1.9%)	7 (2.3%)
Missing DEA Number	1 (1.9%)	11 (3.6%)
Missing Email	1 (1.9%)	2 (0.6%)
Missing NPI Number	1 (1.9%)	8 (2.6%)
Missing Physician Signature Date	0	13 (4.2%)
Missing Signature	0	13 (4.2%)
Missing State License Number	1 (1.9%)	7 (2.3%)
No Attestation	41 (77.4%)	226 (73.1%)
Pending Enrollment Intake	2 (3.8%)	9 (2.9%)
Provided DEA does not have Correct Schedule for this Drug	5 (9.4%)	36 (11.7%)
Training Access Suspended	0	1 (0.3%)
Training Not Complete	28 (52.8%)	184 (59.5%)

[a] Reflects the total number of prescribers pending enrollment in the current reporting period. Prescribers may have attempted enrollment and become pending in another reporting period.

[b] Percentages are based on the total number (N) of prescribers attempting enrollment. Percentages may not add to 100% because a single prescriber may be pending enrollment for more than one reason.

[c] Prescribers may be pending enrollment for more than one reason.

5.1.3 Pharmacy Enrollment, Inactivation, and Education [Metric 6, 7, 8]

There were a total of 28,617 pharmacies newly enrolled or re-enrolled in this reporting period. Of the 5,892 (20.6%) pharmacies that newly enrolled in the TIRF REMS Access program, 5,286 were chain pharmacy stores, 510 were independent outpatient pharmacies, 87 were inpatient pharmacies, and 7 were closed system pharmacy locations. The 7 closed system pharmacies are represented by 7 closed system entities (See Section 5.1.5). A total of 22,725

(79.4%) pharmacies re-enrolled; 21,550 were chain pharmacy stores, 992 were independent outpatient pharmacies, 143 were inpatient pharmacies, and 2 were closed system pharmacy locations (Table 8).

Table 8 Pharmacy Enrollment

Parameter	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015		
	Non-Closed System Pharmacies N (%)	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Total Number of Pharmacies with Enrollment Activity in this Reporting Period	28,607	10	28,617
Total Number of Newly Enrolled Pharmacies	5,885 (20.6%)	7 (70.0%)	5,892 (20.6%)
Inpatient Pharmacies	87 (1.5%)	N/A	87 (1.5%)
Chain Pharmacy Headquarters[c]	2 (<0.1%)	N/A	2 (<0.1%)
Chain Pharmacy Stores	5,286 (89.8%)	N/A	5,286 (89.7%)
Independent Outpatient Pharmacies	510 (8.7%)	N/A	510 (8.7%)
Closed System Headquarters[c]	N/A	0	0 (<0.1%)
Closed System Pharmacies	N/A	7 (100.0%)	7 (0.1%)
Total Number of Re-Enrolled Pharmacies	22,722 (79.4%)	3 (30.0%)	22,725 (79.4%)
Inpatient Pharmacies	143 (0.6%)	N/A	143 (0.6%)
Chain Pharmacy Headquarters[c]	37 (0.2%)	N/A	37 (0.2%)
Chain Pharmacy Stores	21,550 (94.8%)	N/A	21,550 (94.8%)
Independent Outpatient Pharmacies	992 (4.4%)	N/A	992 (4.4%)
Closed System Headquarters[c]	N/A	1 (33.3%)	1 (<0.1%)
Closed System Pharmacies	N/A	2 (66.7%)	2 (<0.1%)
Number of Pharmacies that Remain Enrolled from a Previous Reporting Period	14,361	238	14,599
Inpatient Pharmacies	638 (4.4%)	N/A	638 (4.4%)
Chain Pharmacy Headquarters[c]	42 (0.3%)	N/A	42 (0.3%)
Chain Pharmacy Stores	10,618 (73.9%)	N/A	10,618 (72.7%)
Independent Outpatient Pharmacies	3,063 (21.3%)	N/A	3,063 (21.0%)
Closed System Headquarters[c]	N/A	5 (2.1%)	5 (<0.1%)
Closed System Pharmacies	N/A	233 (97.9%)	233 (1.6%)

Parameter	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015		
	Non-Closed System Pharmacies N (%)	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Total Number of Pharmacies Enrolled as of the End of this Reporting Period	42,968	248	43,216
Inpatient Pharmacies	868 (2.0%)	N/A	868 (2.0%)
Chain Pharmacy Headquarters[c]	81 (0.2%)	N/A	81 (0.2%)
Chain Pharmacy Stores	37,454 (87.2%)	N/A	37,454 (86.7%)
Independent Outpatient Pharmacies	4,565 (10.6%)	N/A	4,565 (10.6%)
Closed System Headquarters[c]	N/A	6 (2.4%)	6 (<0.1%)
Closed System Pharmacies	N/A	242 (97.6%)	242 (0.6%)
Cumulative Number of Pharmacies Ever Enrolled[d,e]	47,348	359	47,707
Inpatient Pharmacies	1,168 (2.5%)	N/A	1,168 (2.4%)
Chain Pharmacy Headquarters[c]	92 (0.2%)	N/A	92 (0.2%)
Chain Pharmacy Stores	39,929 (84.3%)	N/A	39,929 (83.7%)
Independent Outpatient Pharmacies[c]	6,159 (13.0%)	N/A	6,159 (12.9%)
Closed System Headquarters	N/A	7 (1.9%)	7 (<0.1%)
Closed System Pharmacies	N/A	352 (98.1%)	352 (0.7%)

[a] Percentages are based on the total number (N) of pharmacies with enrollment activity in this reporting period.
[b] Pharmacies that are enrolled within this reporting period and were still enrolled at the end of the reporting period.
[c] The number of Chain Pharmacy Headquarters and Closed System Headquarters may not be associated with the number of Chain Pharmacy Stores and Closed System Pharmacies, respectively. Chain Pharmacy Stores or Closed System Pharmacies may be associated with a Headquarter enrolled in a previous reporting period.
[d] Cumulative number of pharmacies from the end of prior period may differ from last period's report due to reconciliation of duplicate records.
[e] One pharmacy is counted as both a Chain Pharmacy Headquarter and a Closed System Headquarter as they transitioned their pharmacy type during this reporting period due to obtaining the ability to electronically adjudicate claims.

As shown in Table 9, there were 4,920 total pharmacies inactivated at least once during the current reporting period including 4,919 non-closed system pharmacies and 1 closed system pharmacy. The non-closed system pharmacies included 4,382 (89.1%) chain pharmacy stores, 422 (8.6%) independent outpatient pharmacies, and 112 (2.3%) inpatient pharmacies.

The reason for most pharmacy inactivations was expired enrollment, which was 33.3% of the inactivated chain pharmacy headquarters and at least 85.7% among inactivated pharmacies in the remaining pharmacy categories. At present, 1,144 pharmacies remained inactivated at the end of this reporting period with 64% never having had any TIRF prescription activity since their initial enrollment in the TIRF REMS Access program. Based on this analysis, there is no barrier to patient access and further outreach is unwarranted.

Table 9 Pharmacy Inactivations

	Current Reporting Period[a] 29OCT2014 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Number of Pharmacies that Became Inactivated During this Reporting Period	4,919	1	4,920
Inpatient Pharmacies	112 (2.3%)	N/A	112 (2.3%)
Chain Pharmacy Headquarters	3 (0.1%)	N/A	3 (0.1%)
Chain Pharmacy Stores	4,382 (89.1%)	N/A	4,382 (89.1%)
Independent Outpatient Pharmacies	422 (8.6%)	N/A	422 (8.6%)
Closed System Pharmacies	N/A	1 (100.0%)	1 (0.0%)
Reason(s) for Inpatient Pharmacy Inactivation[b]			
Program Opt-Out	16 (14.3%)	N/A	16 (14.3%)
Enrollment Expired[c]	96 (85.7%)	N/A	96 (85.7%)
Enrollment remained expired at end of period	68 (70.8%)	N/A	68 (70.8%)
Reason(s) for Chain Pharmacy Headquarters Inactivation[d]			
Program Opt-Out	2 (66.7%)	N/A	2 (66.7%)
Enrollment Expired[c]	1 (33.3%)	N/A	1 (33.3%)
Enrollment remained expired at end of period	0	N/A	0
Reason(s) for Chain Pharmacy Store Inactivation[d]			
Program Opt-Out	87 (2.0%)	N/A	87 (2.0%)
Enrollment Expired[c]	4,295 (98.0%)	N/A	4,295 (98.0%)
Enrollment remained expired at end of period	645 (15.0%)	N/A	645 (15.0%)
Reason(s) for Independent Outpatient Pharmacy Inactivation[e]			
Program Opt-Out	5 (1.2%)	N/A	5 (1.2%)
Enrollment Expired[c]	417 (98.8%)	N/A	417 (98.8%)
Enrollment remained expired at end of period	326 (78.2%)	N/A	326 (78.2%)
Reason(s) For Closed System Pharmacy Inactivation[f]			
Enrollment Expired[c]	N/A	1 (100.0%)	1 (100.0%)

	Current Reporting Period[a] 29OCT2014 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Enrollment remained expired at end of period	N/A	1 (100.0%)	1 (100.0%)
Numbers of Pharmacies Inactivated in This Time Period that Remain Inactivated as of the End of this Reporting Period	1,145	1	1,146
Inpatient Pharmacies	84 (7.3%)	N/A	84 (7.3%)
Chain Pharmacy Headquarters	2 (0.2%)	N/A	2 (0.2%)
Chain Pharmacy Stores	728 (63.6%)	N/A	728 (63.5%)
Independent Outpatient Pharmacies	331 (28.9%)	N/A	331 (28.9%)
Closed System Pharmacies	N/A	1 (100.0%)	1 (0.1%)
Total Number of Pharmacies Inactivated as of the End of This Reporting Period	4,381	111	4,492
Inpatient Pharmacies	300 (6.8%)	N/A	300 (6.7%)
Chain Pharmacy Headquarters	12 (0.3%)	N/A	12 (0.3%)
Chain Pharmacy Stores	2,475 (56.5%)	N/A	2,475 (55.1%)
Independent Outpatient Pharmacies	1,594 (36.4%)	N/A	1,594 (35.5%)
Closed System Pharmacies	N/A	111 (100.0%)	111 (2.5%)
Cumulative Number of Pharmacies Ever Inactivated[g]	12,289	168	12,457
Inpatient Pharmacies	453 (3.7%)	N/A	453 (3.6%)
Chain Pharmacy Headquarters	23 (0.2%)	N/A	23 (0.2%)
Chain Pharmacy Stores	9,476 (77.1%)	N/A	9,476 (76.1%)
Independent Outpatient Pharmacies	2,337 (19.0%)	N/A	2,337 (18.8%)
Closed System Pharmacies	N/A	168 (100.0%)	168 (1.3%)

[a] Pharmacies with 'inactive' status at least once during the reporting period.

[b] Percentages are based on the total number (N) of inactivated inpatient pharmacies. An inpatient pharmacy may have more than one reason for inactivation.

[c] Pharmacies whose status is 'Inactive-Expired' at any time during the enrollment period.

[d] Percentages are based on the total number (N) of inactivated chain pharmacy headquarters or chain pharmacy stores. A chain pharmacy headquarters or chain pharmacy store may have more than one reason for inactivation.

[e] Percentages are based on the total number (N) of inactivated independent outpatient pharmacy stores. An independent outpatient pharmacy store may have more than one reason for inactivation.

[f] Percentages are based on the total number (N) of inactivated closed system pharmacies. A closed system pharmacy may have more than one reason for inactivation.

[g] Cumulative is sum of all reporting period totals.

During the current reporting period, there were 44 pharmacies that attempted enrollment but enrollment was pending 3 to 6 months later. As of the end of the reporting period, there were a total of 198 pharmacies pending enrollment for 6 months or longer. Pharmacies may have attempted enrollment and become pending in another reporting period.

For pharmacies pending enrollment for 3 to 6 months, the most frequent reasons were pending test transaction verification (63.6%), no attestation (34.1%), and training not complete (22.7%).

For pharmacies pending enrollment for 6 months or longer, the most frequent reasons were similar and included pending test transaction verification (52.0%), no attestation (44.9%), and training not complete (35.9%).

The number of pharmacies that attempted enrollment but are still pending enrollment for 3 to 6 months or longer than 6 months, and the reasons for pending enrollment are shown in Table 10.

Table 10 Pharmacies Pending Enrollment

Parameter	Current Reporting Period[a] 29OCT2014 to 28OCT2015					
	Pharmacies Pending Enrollment ≥3 - 6Months[b]			Pharmacies Pending Enrollment: >6 Months[b]		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Pharmacies that Attempted Enrollment but are Still Pending Enrollment[c]	44	0	44	198	0	198
Reasons for Pending Enrollment						
Invalid DEA	2 (4.5%)	0	2 (4.5%)	6 (3.0%)	0	6 (3.0%)
Invalid NCPDP	1 (2.3%)	0	1 (2.3%)	4 (2.0%)	0	4 (2.0%)
Invalid NPI	1 (2.3%)	0	1 (2.3%)	3 (1.5%)	0	3 (1.5%)
Knowledge Assessment Failure - First Attempt	1 (2.3%)	0	1 (2.3%)	6 (3.0%)	0	6 (3.0%)
Knowledge Assessment Failure - Third Attempt	1 (2.3%)	0	1 (2.3%)	1 (0.5%)	0	1 (0.5%)
Missing DEA Number	0	0	0	1 (0.5%)	0	1 (0.5%)
No Attestation	15 (34.1%)	0	15 (34.1%)	89 (44.9%)	0	89 (44.9%)
Pending Enrollment Intake	1 (2.3%)	0	1 (2.3%)	6 (3.0%)	0	6 (3.0%)
Pending Test Transaction Verification	28 (63.6%)	0	28 (63.6%)	103 (52.0%)	0	103 (52.0%)
Switch Provider Contract Not Signed	0	0	0	1 (0.5%)	0	1 (0.5%)
Training Not Complete	10 (22.7%)	0	10 (22.7%)	71 (35.9%)	0	71 (35.9%)

[a] Reflects the total number of pharmacies pending enrollment in the current reporting period. Pharmacies may have attempted enrollment and became pending in another reporting period.

[b] Percentages are based on the total number (N) of pharmacies attempting enrollment. Percentages may not add up to 100% because a single pharmacy may be pending enrollment for more than one reason.

[c] Pharmacies may be pending enrollment for more than one reason.

5.1.4 Wholesaler/Distributor Enrollment [Metric 9 and 10]

During the current reporting period, 3 (18.8%) wholesalers/distributors newly enrolled in the REMS program and 13 (81.3%) re-enrolled (Table 11).

There were 3 wholesalers/distributors inactivated during the current reporting period due to enrollment expiration and 2 had not re-enrolled by the end of the reporting period (Table 12). Both distributors who remained inactivated at the end of the reporting period were acquired by other entities.

Table 11 Distributor Enrollment

	Current Reporting Period[a] 29OCT2014 to 28OCT2015
Parameter	**N (%)**
Number of Distributors with Enrollment Activity in This Reporting Period	16
Number of Newly Enrolled Distributors	3 (18.8%)
Number of Re-Enrolled Distributors	13 (81.3%)
Number of Distributors that Remain Enrolled from Previous Reporting Periods	21
Total Number of Distributors Enrolled as of the End of the Reporting Period	37
Cumulative Number of Distributors Ever Enrolled[c]	48

[a] Percentages are based on the total number (N) for the relevant Distributors for the period.
[b] Includes Distributors that transitioned into the TIRF REMS Access program from other individual REMS programs.
[c] Cumulative Distributors from the end of prior period may differ from last period's report due to reconciliation of duplicate Distributors.

Table 12 Distributor Inactivations

	Current Reporting Period[a] 29OCT2014 to 28OCT2015
Parameter	**N (%)**
Number of Distributors that Became Inactivated in This Reporting Period	3
Reason(s) for Distributor Inactivation	
Enrollment Expired[b]	3 (100.0%)
Enrollment remained expired at end of period	2 (66.7%)
Number of Distributors that Remain Inactivated From Previous Reporting Periods	9
Total Number of Distributors Inactivated as of the End of the Reporting Period	11
Cumulative Number of Distributors Ever Inactivated[c,d]	17

[a] Percentages are based on the total number (N) for the relevant inactivated Distributors for the period.
[b] Distributors with 'inactive' status at least once during the reporting period.
[c] Distributors whose status is 'Inactive-Expired' at any time during the enrollment period.
[d] Cumulative is sum of all reporting period totals.

5.1.5 Dispensing Activity [Metric 11, 12, 13,]

A total of 152,686 prescriptions were adjudicated for safety by the TIRF REMS Access program in the current reporting period including 152,228 prescriptions from non-closed system pharmacies and 458 from closed system pharmacies (Table 13). Of the total prescriptions, 94.2% were subsequently approved for dispensing without encountering any REMS-related rejections (i.e., were authorized for dispensing by insurance or cash bin).

Table 13 Prescriptions from Outpatient Pharmacies That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing

	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Number of Unique Prescriptions Submitted for Authorization	152,228	458	152,686	558,038	3,037	561,075
Total Number of Unique Prescriptions That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing	143,365 (94.2%)	398 (86.9%)	143,763 (94.2%)	498,591 (89.3%)	2,415 (79.5%)	501,006 (89.3%)
Independent Pharmacies	107,430 (70.6%)	N/A	107,430 (70.4%)	329,849 (59.1%)	N/A	329,849 (58.8%)
Chain Pharmacies	35,935 (23.6%)	N/A	35,935 (23.5%)	168,742 (30.2%)	N/A	168,742 (30.1%)
Closed System Pharmacies	N/A	398 (86.9%)	398 (0.3%)	N/A	2,415 (79.5%)	2,415 (0.4%)

[a] Prescriptions successfully adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or cash bin (bin number).
[b] Percentages are based on the total number (N) of unique prescriptions that never encountered a REMS-related rejection for the reporting period.
[c] Includes authorizations from all pharmacies that were enrolled in the TIRF REMS Access program at any time from inception of the program.

When a prescription is presented it must meet the REMS edit requirements before it may be authorized for dispensing, or it is rejected. The reasons why a prescription will not meet a REMS edit requirement are included in Table 14.

If a prescription is rejected, the pharmacy must contact the TIRF REMS Access program to rectify the rejected transaction. Upon receiving an inbound call from a pharmacy provider, the TIRF REMS Access program Call Center Service Representative (CSR) works to resolve the rejected transaction and to provide instructions on the corrective action needed to successfully process the transaction. Corrective action includes outreach and education to remedy rejected transaction processing. Of the 152,686 unique prescriptions submitted for approval during the current reporting period, 1,735 prescriptions encountered at least one REMS-related rejection prior to being authorized for dispensing from outpatient pharmacies (Table 15). There were a total of 7,188 prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing (Table 16).

Table 14 Reasons for Prescriptions Not Meeting REMS Edit Requirements

Reason	Description
Prescriber ID Not Enrolled/Not Found	Found the prescriber last name but not the NPI, DEA or State License Number or both prescriber last name and ID are not found
PPAF Incomplete	Patient's PPAF is in an complete status; the PPAF is missing information
Patient Zip Code Missing	Patient's zip code was not submitted on the transaction
Prescriber Last Name Did Not Match Name Registered	Prescriber last name on the transaction did not match the prescriber last name associated with the Prescriber ID
Pharmacy Not Enrolled	Pharmacy is not enrolled; the pharmacy has not completed the enrollment or re-enrollment process
Prescriber ID not registered	Found the prescriber last name but the NPI, DEA or State License Number does not match prescriber.
PPAF expired	Patient's PPAF expired. (i.e. no prescription activity for 6 months)
PPAF terminated	Patient's PPAF terminated (2 year expiration)
Prescriber is terminated	Prescriber enrollment terminated.
Pharmacy terminated	Pharmacy enrollment terminated

Table 15 presents the results for the prescriptions that encountered at least one REMS-related rejection prior to being authorized for dispensing from outpatient pharmacies. The most frequent rejection reasons for independent pharmacies (n=1,254) were zip code missing (25.3%), PPAF incomplete (24.0%), Prescriber ID not registered (17.4%), Prescriber last name did not match register (12.8%), PPAF expired (9.4%), and PPAF terminated (9.1%).

The most frequent rejection reasons for chain pharmacies (n=481) were Prescriber last name did not match registered (27.0%), Prescriber ID not registered (24.5%), PPAF incomplete (16.2%), PPAF terminated (11.0%), PPAF expired (9.4%), zip code missing (8.3%), and Prescriber is terminated (8.1%).

No prescriptions from closed system pharmacies encountered a REMS-related rejection prior to being authorized for dispensing in the current reporting period.

Table 16 presents the results for the prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing from outpatient pharmacies. As stated previously, of the 152,686 unique prescriptions submitted for approval during the current reporting period there were a total of 7,188 prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing.

The most frequent rejection reasons for independent pharmacies (n=3,959) were Prescriber ID not registered (38.7%), zip code missing (26.1%), Prescriber last name did not match registered (12.8%), Prescriber is terminated (12.0%).

The most frequent rejection reasons for chain pharmacies (n=3,169) were Prescriber ID not registered (53.4%), Prescriber last name did not match registered (21.5%), Prescriber is terminated (10.5%), and zip code missing (8.2%).

The most frequent rejection reasons for closed system pharmacies (n=60) were Prescriber ID not registered (41.7%), Pharmacy terminated (21.7%), Prescriber last name did not match registered (16.7%), and Prescriber is terminated (13.3%).

Table 15 Prescriptions from Outpatient Pharmacies That Encountered at Least One REMS-Related Rejection Prior to Being Authorized for Dispensing

Parameter	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Number of Unique Prescriptions Submitted for Authorization	152,228	458	152,686	558,038	3,037	561,075
Total Number of Unique Prescriptions that encountered At Least One Initial REMS-Related Rejection Prior to being Authorized for Dispensing	1,735 (1.1%)	0	1,735 (1.1%)	18,576 (3.3%)	57 (1.9%)	18,633 (3.3%)
Independent Pharmacies	1,254 (0.8%)	N/A	1,254 (0.8%)	13,432 (2.4%)	N/A	13,432 (2.4%)
Chain Pharmacies	481 (0.3%)	N/A	481 (0.3%)	5,144 (0.9%)	N/A	5,144 (0.9%)
Closed System Pharmacies	N/A	0	0	N/A	57 (1.9%)	57 (<0.1%)
Independent Pharmacies						
Reason(s) for Rejection[d]						
Zip Code Missing	317 (25.3%)	N/A		6,475 (48.2%)	N/A	
PPAF Incomplete	301 (24.0%)	N/A		3,648 (27.2%)	N/A	
Prescriber last name did not match registered	161 (12.8%)	N/A		1,839 (13.7%)	N/A	
PrescriberID not registered	218 (17.4%)	N/A		1,621 (12.1%)	N/A	
PPAF terminated	114 (9.1%)	N/A		885 (6.6%)	N/A	
PPAF Expired	118 (9.4%)	N/A		680 (5.1%)	N/A	
Prescriber is terminated	77 (6.1%)	N/A		280 (2.1%)	N/A	
Last Name and DOB Missing	14 (1.1%)	N/A		208 (1.5%)	N/A	
PrescriberID not submitted	29 (2.3%)	N/A		128 (1.0%)	N/A	

Parameter	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Pharmacy terminated	8 (0.6%)	N/A		116 (0.9%)	N/A	
First Name Missing	7 (0.6%)	N/A		68 (0.5%)	N/A	
Prescriber Terminated and Last Name Mismatch	6 (0.5%)	N/A		27 (0.2%)	N/A	
DOB Missing	6 (0.5%)	N/A		24 (0.2%)	N/A	
First Name, Last Name, and Zip Code Missing	0	N/A		24 (0.2%)	N/A	
Zip Code and Last Name	0	N/A		13 (0.1%)	N/A	
First Name and Last Name Missing	1 (0.1%)	N/A		10 (0.1%)	N/A	
DOB and Zip Code Missing	1 (0.1%)	N/A		9 (0.1%)	N/A	
Last Name Missing	0	N/A		2 (<0.1%)	N/A	
Database Failure - System Unavailable due to maintenance	0	N/A		1 (<0.1%)	N/A	
First Name, Last Name and DOB Missing	0	N/A		1 (<0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	0	N/A		1 (<0.1%)	N/A	
Multi-Match - two or more patient match on same criteria	0	N/A		1 (<0.1%)	N/A	
Chain Pharmacy Stores						
Reason(s) for Rejection[d]						
PPAF Incomplete	78 (16.2%)	N/A		2,180 (42.4%)	N/A	
PrescriberID not registered	118 (24.5%)	N/A		1,087 (21.1%)	N/A	
Zip Code Missing	40 (8.3%)	N/A		860 (16.7%)	N/A	
PPAF terminated	53 (11.0%)	N/A		517 (10.1%)	N/A	
Prescriber last name did not match registered	130 (27.0%)	N/A		506 (9.8%)	N/A	

Parameter	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
PPAF Expired	45 (9.4%)	N/A		394 (7.7%)	N/A	
Prescriber is terminated	39 (8.1%)	N/A		113 (2.2%)	N/A	
First Name Missing	9 (1.9%)	N/A		56 (1.1%)	N/A	
Last Name and DOB Missing	8 (1.7%)	N/A		40 (0.8%)	N/A	
Pharmacy terminated	6 (1.2%)	N/A		26 (0.5%)	N/A	
PrescriberID not submitted	2 (0.4%)	N/A		19 (0.4%)	N/A	
First Name and Last Name Missing	0	N/A		7 (0.1%)	N/A	
DOB Missing	0	N/A		6 (0.1%)	N/A	
First Name, Last Name, and Zip Code Missing	0	N/A		6 (0.1%)	N/A	
Multi-Match - two or more patient match on same criteria	0	N/A		3 (0.1%)	N/A	
Prescriber Terminated and Last Name Mismatch	0	N/A		3 (0.1%)	N/A	
First Name, Last Name and DOB Missing	0	N/A		2 (<0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	0	N/A		2 (<0.1%)	N/A	
Pharmacy not Registered	0	N/A		2 (<0.1%)	N/A	
DOB and Zip Code Missing	0	N/A		1 (<0.1%)	N/A	
Database Failure - System unavailable due to system maintenance	0	N/A		1 (<0.1%)	N/A	
First Name and DOB Missing	0	N/A		1 (<0.1%)	N/A	
Last Name Missing	1 (0.2%)	N/A		1 (<0.1%)	N/A	
Re-register	0	N/A		1 (<0.1%)	N/A	

Parameter	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Closed System Pharmacies						
Reason(s) for Rejection[d]						
Zip Code Missing	N/A	0		N/A	33 (57.9%)	
PPAF Incomplete	N/A	0		N/A	10 (17.5%)	
PrescriberID not registered	N/A	0		N/A	9 (15.8%)	
PPAF terminated	N/A	0		N/A	6 (10.5%)	
Prescriber last name did not match registered	N/A	0		N/A	6 (10.5%)	
PPAF Expired	N/A	0		N/A	3 (5.3%)	

[a] Prescription successfully adjudicated for safety (i.e., successful REMS edit).and authorized for dispensing by insurance or cash bin (bin number).
[b] Percentages are based on the total number (N) of number of unique prescriptions that encountered at least one initial REMS-related rejection prior to being authorized for dispensing for the reporting period.
[c] Includes authorizations from pharmacies that transitioned into the TIRF REMS Access program from other individual REMS programs.
[d] Prescriptions can be rejected for more than one reason.

Table 16 Prescriptions That Encountered at Least One REMS-Related Rejection and Never Authorized for Dispensing from Outpatient Pharmacies

	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Number of Unique Prescriptions Submitted for Authorization	152,228	458	152,686	558,038	3,037	561,075
Total Number of Unique Prescriptions that encountered At Least One Initial REMS-Related Rejection and Never Authorized for Dispensing	7,128 (4.7%)	60 (13.1%)	7,188 (4.7%)	40,871 (7.3%)	565 (18.6%)	41,436 (7.4%)
Independent Pharmacies	3,959 (2.6%)	N/A	3,959 (2.6%)	20,117 (3.6%)	N/A	20,117 (3.6%)
Chain Pharmacies	3,169 (2.1%)	N/A	3,169 (2.1%)	20,754 (3.7%)	N/A	20,754 (3.7%)
Closed System Pharmacies	N/A	60 (13.1%)	60 (<0.1%)	N/A	565 (18.6%)	565 (0.1%)
Independent Pharmacies						
Reason(s) for Rejection[d]						
PrescriberID not registered	1,533 (38.7%)	N/A		9,632 (47.9%)	N/A	
Prescriber last name did not match registered	753 (19.0%)	N/A		3,891 (19.3%)	N/A	
Zip Code Missing	1,032 (26.1%)	N/A		2,357 (11.7%)	N/A	
PPAF Incomplete	137 (3.5%)	N/A		2,087 (10.4%)	N/A	
Prescriber is terminated	476 (12.0%)	N/A		1,691 (8.4%)	N/A	
Pharmacy terminated	104 (2.6%)	N/A		665 (3.3%)	N/A	
PPAF terminated	68 (1.7%)	N/A		412 (2.0%)	N/A	
PrescriberID not submitted	100 (2.5%)	N/A		410 (2.0%)	N/A	
PPAF Expired	44 (1.1%)	N/A		250 (1.2%)	N/A	

	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Last Name and DOB Missing	44 (1.1%)	N/A		101 (0.5%)	N/A	
Prescriber Terminated and Last Name Mismatch	28 (0.7%)	N/A		95 (0.5%)	N/A	
First Name Missing	17 (0.4%)	N/A		46 (0.2%)	N/A	
Multi-Match - two or more patient match on same criteria	3 (0.1%)	N/A		8 (<0.1%)	N/A	
First Name, Last Name, and Zip Code Missing	4 (0.1%)	N/A		7 (<0.1%)	N/A	
DOB Missing	2 (0.1%)	N/A		3 (<0.1%)	N/A	
First Name and Last Name Missing	3 (0.1%)	N/A		3 (<0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	0	N/A		2 (<0.1%)	N/A	
Last Name Missing	0	N/A		1 (<0.1%)	N/A	
Zip Code and Last Name	0	N/A		1 (<0.1%)	N/A	
Chain Pharmacies						
Reason(s) for Rejection[d]						
PrescriberID not registered	1,691 (53.4%)	N/A		13,578 (65.4%)	N/A	
Prescriber last name did not match registered	682 (21.5%)	N/A		2,463 (11.9%)	N/A	
PPAF Incomplete	77 (2.4%)	N/A		2,245 (10.8%)	N/A	
Prescriber is terminated	332 (10.5%)	N/A		1,434 (6.9%)	N/A	
Pharmacy terminated	70 (2.2%)	N/A		409 (2.0%)	N/A	
PPAF terminated	61 (1.9%)	N/A		379 (1.8%)	N/A	
Zip Code Missing	260 (8.2%)	N/A		371 (1.8%)	N/A	
PrescriberID not submitted	34 (1.1%)	N/A		240 (1.2%)	N/A	
PPAF Expired	36 (1.1%)	N/A		230 (1.1%)	N/A	

	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Last Name and DOB Missing	59 (1.9%)	N/A		67 (0.3%)	N/A	
First Name Missing	31 (1.0%)	N/A		61 (0.3%)	N/A	
Prescriber Terminated and Last Name Mismatch	14 (0.4%)	N/A		28 (0.1%)	N/A	
Multi-Match - two or more patient match on same criteria	0	N/A		11 (0.1%)	N/A	
First Name and Last Name Missing	0	N/A		10 (<0.1%)	N/A	
Pharmacy not Registered	0	N/A		10 (<0.1%)	N/A	
Last Name Missing	4 (0.1%)	N/A		4 (<0.1%)	N/A	
DOB and Zip Code Missing	0	N/A		1 (<0.1%)	N/A	
Database Failure - System unavailable due to system maintenance	0	N/A		1 (<0.1%)	N/A	
Closed System Pharmacies						
Reason(s) for Rejection[d]						
PrescriberID not registered	N/A	25 (41.7%)		N/A	307 (54.3%)	
Prescriber last name did not match registered	N/A	10 (16.7%)		N/A	103 (18.2%)	
PPAF Incomplete	N/A	2 (3.3%)		N/A	55 (9.7%)	
Pharmacy terminated	N/A	13 (21.7%)		N/A	41 (7.3%)	
Prescriber is terminated	N/A	8 (13.3%)		N/A	34 (6.0%)	
Zip Code Missing	N/A	1 (1.7%)		N/A	28 (5.0%)	
PPAF terminated	N/A	1 (1.7%)		N/A	4 (0.7%)	
PPAF Expired	N/A	1 (1.7%)		N/A	2 (0.4%)	
Multi-Match - two or more patient match on same criteria	N/A	0		N/A	1 (0.2%)	

	Current Reporting Period[a,b] 29OCT2014 to 28OCT2015			Cumulative[a,b,c] 28DEC2011 to 28OCT2015		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Prescriber Terminated and Last Name Mismatch	N/A	0		N/A	1 (0.2%)	
PrescriberID not submitted	N/A	0		N/A	1 (0.2%)	

[a] Prescription successfully adjudicated for safety (i.e., successful REMS edit).and authorized for dispensing by insurance or cash bin (bin number).
[b] Percentages are based on the total number (N) of number of unique prescriptions that encountered at least one initial REMS-related rejection prior to being authorized for dispensing for the reporting period.
[c] Includes authorizations from pharmacies that transitioned into the TIRF REMS Access program from other individual REMS programs.
[d] Prescriptions can be rejected for more than one reason.

In the 36-Month FDA Assessment Report Acknowledgement Letter, the FDA remarked that there was a notable increase in mean and median prescription processing times during the 36-month reporting period versus the previous reporting period. The FDA requested that TRIG investigate and identify the causes of these increasing delays in prescription processing and report the results in the 48-month assessment report.

For all pharmacies, the mean time to authorization for a prescription that experienced at least one initial REMS-related rejection was 6.7 days while the median time was 1.3 days (Table 17). For chain pharmacy stores it took a mean of 7.8 days (median 2.2 days) compared with independent outpatient pharmacies that took a mean of 6.3 days (median 1.0 day). There were no inpatient or closed system pharmacies with data to report in the current reporting period as no REMS-related rejections were received by these pharmacies. The increase in the mean time to authorization between chain and independent pharmacies may be primarily due to the relatively low number of prescriptions with at least one initial REMS-related rejection (n=1,735 [1.1%]). For comparison, in the 36-month report the number of prescriptions with at least one initial REMS-related rejection was 3,738 (2.3% of total prescriptions).

Table 17 Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection

	Current Reporting Period 29OCT2014 to 28OCT2015	Cumulative 28DEC2011 to 28OCT2015
Total Mean Time For Prescription to be Authorized[a] (Days)[b]	6.683	3.647
Inpatient Pharmacies	--	--
Chain Pharmacy Stores	7.805	4.382
Independent Outpatient Pharmacies	6.253	3.354
Closed System Pharmacies	--	6.291
Total Median Time For Prescription to be Authorized[a] (Days)	1.320	0.213
Inpatient Pharmacies	--	--
Chain Pharmacy Stores	2.171	1.036
Independent Outpatient Pharmacies	1.031	0.089
Closed System Pharmacies	--	1.124

[a] Prescriptions included were resolved in the current reporting period. Prescriptions may have been initially rejected in a previous reporting period.

[b] Time to authorization for a prescription that experienced at least one initial REMS-related rejection excludes prescriptions processed through the inpatient pharmacy process.

As described in Section 5.1.3., a total of 7 closed-system pharmacy entities were enrolled in the TIRF REMS Access program during this reporting period. These entities include:

- (b) (4)
- National Institutes of Health Clinical Center Pharmacy
- U.S. Department of Veterans Affairs
- (b) (4)
- DLA Troop Support
- (b) (4)

During the current reporting period, a total of 398 prescription authorizations were provided through these closed system pharmacy locations (Table 18). During this reporting period on 18 May 2015, (b) (4) transitioned from being a closed-system pharmacy to a non-closed system pharmacy due to the pharmacy obtaining the ability to electronically adjudicate claims. Therefore, the prescription authorizations described in Table 18 for (b) (4) only represent prescriptions processed prior to this transition.

Table 18 Number of Prescription Authorizations per Closed System Pharmacy

	Current Reporting Period 29OCT2014 to 28OCT2015	Cumulative 28DEC2011 to 28OCT2015
Total Number of Closed System Pharmacy Prescription Authorizations	398	2,472
(b) (4)	(b) (4)	

	Current Reporting Period 29OCT2014 to 28OCT2015	Cumulative 28DEC2011 to 28OCT2015
(b) (4)		
(b) (4)		

	Current Reporting Period 29OCT2014 to 28OCT2015	Cumulative 28DEC2011 to 28OCT2015
(b) (4)		

[a] During this reporting period on 18 May 2015, (b) (4) changed from a closed system pharmacy to a non-closed system pharmacy.

In the 36-Month FDA Assessment Report Acknowledgement Letter, the FDA requested that the closed-system pharmacies authorization process be re-evaluated as to whether a novel authorization process was warranted or technically feasible and report the conclusions in the 48-month assessment report. The TRIG has determined that the current prescription authorization volume for closed-system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time. The TRIG will continue to monitor and assess the need for an alternate solution as appropriate.

5.1.6 Barriers or Delays in Patient Access [Metric 14 and 15]

Prescriptions Dispensed Within First 10 Days after Patient Enrollment

Across all pharmacies, a total of 8,101 prescriptions were dispensed to 6,715 patients within the first 10 days after patient enrollment (Table 19). The majority of patients (n=6,702) were dispensed prescriptions by non-closed system pharmacies (8,087 prescriptions). Of the 2,059 patients who received prescriptions without a PPAF, the majority of patients (30.7%) received only 1 fill without a PPAF. A total of 8 patients received 3 prescriptions within 10 days without a PPAF on file. All 8 patients had their prescriptions filled through non-closed system pharmacies.

During this reporting period, it was observed that 1 patient potentially received more than 3 fills within the 10-day period without a PPAF on file from a non-closed system pharmacy.

48-Month Assessment Report Update

In the 36-month assessment report, it was reported that 4 patients received more than 3 prescriptions within 10 days without a PPAF on file. All 4 patients had their prescriptions filled through non-closed system pharmacies. Upon review of all 4 patients' prescription

instances and detail, it was verified that none of the 4 patients received more than 3 prescriptions within 10 days without a PPAF on file.

For Patients 1 through 3, the same independent outpatient pharmacy submitted duplicate prescriptions that did not count towards the 10-day period and also submitted reversal prescriptions for these claims. Since the prescription status did not change, it first appeared that the patients received multiple prescriptions when in fact they had not. It was confirmed that the 3 patients received only 3 unique prescriptions each within the 10 day period.

For Patient 4, a different independent outpatient pharmacy submitted 4 prescriptions. Three prescriptions were batched billed from the pharmacy's pharmacy management system simultaneously, causing the prescriptions to pass through the REMS edits sub-seconds apart. Since a patient record was not found, the patient was passively enrolled in the TIRF REMS Access program 3 times. A fourth prescription was submitted and subsequently reversed. Ultimately, it was confirmed that the patient received only 3 unique prescriptions within the 10-day period.

The data indicate these are isolated incidents that happened over 3 days and at 2 separate independent outpatient pharmacies. Both pharmacies were contacted and the pharmacists verbally confirmed that each patient did not receive greater than 3 prescriptions in the 10-day period. The pharmacists were re-educated on the TIRF REMS Access program prescription process. PPAFs were appropriately submitted for all 4 patients.

Table 19 Prescriptions Dispensed During the First 10 Days after Passive Patient Enrollment

	Current Reporting Period 29OCT2014 to 28OCT2015				Cumulative[a,b] 28DEC2011 to 28OCT2015			
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Combined Pharmacies[d] N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Combined Pharmacies[d] N (%)**	**Total Pharmacies N (%)**
Number of prescriptions dispensed during the first 10 days after patient enrollment	8,087	14	0	8,101	37,444	211	11	37,666
Number of patients dispensed a prescription during the first 10 days after enrollment	6,702	13	0	6,715	31,249	174	5	31,428
With PPAF[b]								
1 Fill	3,704 (55.3%)	5 (38.5%)	0	3,709 (55.2%)	13,373 (42.8%)	53 (30.5%)	1 (20.0%)	13,427 (42.7%)
2 Fills	770 (11.5%)	1 (7.7%)	0	771 (11.5%)	2,606 (8.3%)	9 (5.2%)	0	2,615 (8.3%)
3 Fills	104 (1.6%)	0	0	104 (1.5%)	380 (1.2%)	1 (0.6%)	0	381 (1.2%)
>3 Fills	18 (0.3%)	0	0	18 (0.3%)	80 (0.3%)	2 (1.1%)	0	82 (0.3%)
Without PPAF[b,c]								
1 Fill	2,052 (30.6%)	7 (53.8%)	0	2,059 (30.7%)	13,971 (44.7%)	100 (57.5%)	1 (20.0%)	14,072 (44.8%)
2 Fills	188 (2.8%)	0	0	188 (2.8%)	1,333 (4.3%)	5 (2.9%)	3 (60.0%)	1,341 (4.3%)
3 Fills	8 (0.1%)	0	0	8 (0.1%)	223 (0.7%)	4 (2.3%)	1 (20.0%)	228 (0.7%)
>3 Fills	1 (<0.1%)	0	0	1 (<0.1%)	10 (<0.1%)	0	0	10 (<0.1%)

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

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

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

[d] Patients who have filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

Prescriptions Dispensed Beyond 10 Days after Patient Enrollment

The TIRF REMS Access program requires that each patient have a PPAF submitted to the TIRF REMS Access program by their prescriber within 10 days of their passive enrollment in order to continue to receive a TIRF medicine. Table 20 below shows the number of prescriptions dispensed beyond the first 10 days without a PPAF on file. From the inception of the TIRF REMS through the current reporting period, 759 prescriptions have been dispensed beyond the first 10 days without a PPAF; only 1 prescription was reported in the current reporting period. TRIG is currently researching the root cause for this 1 prescription that was dispensed beyond 10 days after patient enrollment, and the findings will be reported in the 60-month report.

Table 20 Prescriptions Dispensed Beyond the First 10 Days after Passive Patient Enrollment Without a PPAF

	Current Reporting Period 29OCT2014 to 28OCT2015				Cumulative[a,b] 28DEC2011 to 28OCT2015			
Parameter	Filled at Non-Closed System Pharmacies N (%)	Filled at Closed System Pharmacies N (%)	Filled at Combined Pharmacies[b] N (%)	Filled at All Pharmacies N (%)	Filled at Non-Closed System Pharmacies N (%)	Filled at Closed System Pharmacies N (%)	Filled at Combined Pharmacies[b] N (%)	Filled at All Pharmacies N (%)
Fills beyond the first 10 days Without PPAF	1	0	0	1	724	32	3	759

[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.
[b] A patient who has filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

5.2 Program Infrastructure and Performance [Metrics 16, 17, 18, 19]

5.2.1 Backup System for Prescription Validation [Metric 16]

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

5.2.2 System Interruptions/Errors and Corrective Actions [Metric 17, 19]

There were no unintended system interruptions during this reporting period [Metric 17].

There was one report of unintended system interruptions that occurred in this reporting period [Metric 19].

A brief summary of this issue identified as a system error/problem and the corrective action is presented below.

System Error and Corrective Action #1 (#23):

Description

On 15 November 2013, 16 patients were identified who had a PPAF expired that received prescriptions outside the grace period requirements. The grace period requirement states that a patient can receive a maximum of 3 prescriptions within 10-day duration after PPAF expiration. The grace period begins once the patient receives their first prescription after the PPAF has expired.

Root Cause

Inadequate communication of pending action defined during TRIG-vendor meeting on 16 November 2011.

Containment

On 17 March 2015, system updates were completed to allow for multiple PPAF expirations per patient to initiate the grace period rather than rejecting claims received after the second and subsequent PPAF expirations.

Correction

The REMS program Change Management Process document needed to clearly identify and track program change inputs and requestors was completed on 15 September 2012. The Product Change Request Procedure SOP-OP-005 was published, and monitoring since that time showed no missed actions/inputs to prompt offering change. No additional violations of the REMS requirements have been reported to date since the problem was identified.

Resolution

Prior to completion of the system updates, on 10 January 2014, all 16 patients, originally reported with expired PPAFs, were confirmed to have a current PPAF on file.

5.2.3 REMS Call Center [Metric 18]

Table 21 below shows reasons for contacting the REMS Call Center by frequency (%). For presentation in the report, this table includes at least 80% of the total cumulative frequency. The most frequent reasons classified under the call reason were pharmacy claim rejection (18.9%), enrollment status inquiry (15.7%), PPAF status inquiry (10.3%), and Web portal logon assistance (8.3%). The call reasons listed below in Table 21 represent 80.6% of calls to the Call Center for the current reporting period.

Table 21 Current Assessment Period Contact Reasons

Reason	Count	Percent[a]
Pharmacy: Pharmacy Claim Rejection	3,300	18.9%
Enrollment Status Inquiry	2,746	15.7%
PPAF Inquiry	1,796	10.3%
Web Portal Logon Assistance	1,448	8.3%
Identifier Issues	948	5.4%
Other/Miscellaneous	909	5.2%
Enrollment Form	890	5.1%
General Program Questions	872	5.0%
Relay Health Transfer – Tier 2 Support	663	3.8%
Potential Adverse Event	501	2.9%

[a] The total percentage presented in the table account for 80.6% of all reasons for contacting the Call Center.

There were no REMS- related barriers reported to the REMS Call Center to report during this reporting period.

6 TIRF REMS ACCESS PROGRAM NON-COMPLIANCE

In the 36-month FDA Report Assessment Acknowledgement Letter, FDA requested that the criteria as to how compliance decisions are made by the NCRT be included with the 48-month assessment report, along with the Non-Compliance Protocol (Appendix 12.1).

FDA also commented that the presentation of non-compliance data in the 36-month assessment report was disorganized. Events found in one non-compliance section of the report sounded similar to events reported in other areas, and thus it was unclear whether these different sources were referring to distinct events or were describing the same event. In addition, while the non-compliance activity table indicated seven instances where closed system pharmacies dispensed drugs without obtaining authorization, the audit conducted by the TRIG reported 513 such incidents. The FDA requested that this section be organized and harmonized with these various components into one clear presentation that was comprehensive and eliminates duplication.

Given this feedback, the non-compliance section was reorganized and clarifying text has been added throughout Section 6, to allow for clean interpretation of the data and events that took place during this reporting period.

Non-compliance is reported via four methods within this assessment report.

1. Stakeholder Non-Compliance Table: Non-compliance cases that have been identified during this reporting period by any stakeholder are counted in the table in Section 6.1, Table 22.
2. Stakeholder Non-Compliance Narratives: Stakeholders who are associated with instances of non-compliance resulting from an NCRT "Warning" or any assessment monitoring are described via non-compliance narrative in Section 6.1, Table 23.
3. CSP Audit Results: Non-compliance cases identified through the CSP audits are described via audit summary in Section 6.2.1.
4. Inpatient Hospital Pharmacy Audit Results: Non-compliance cases identified through the inpatient audits would be described via audit summary in Section 6.2.2; however, no non-compliance was identified through these audits and therefore no audit summaries have been included.

These four methods of reporting non-compliance are additive in nature. Non-compliance cases discussed within the audit sections or the non-compliance narratives are not counted within the non-compliance table. Prescribers or pharmacies represented in the table are not described in the audit sections or the non-compliance narrative table.

6.1 Stakeholder Non-Compliance [Metric 23, 24, 25, 26, 27, 28]

Each unique stakeholder non-compliance case is investigated and non-compliance activity is generally reported two ways during a reporting period, either as a confirmed non-compliance activity report as in Table 22 or it is described in a narrative as in Table 23. If single non-compliance cases are reported over time and appear, for example, in Table 22 for two consecutive assessment reports, the Stakeholder's third offense will warrant a CAP and then all offenses are reported in a narrative only, and not in Table 22. Any confirmed non-compliance event that results in an NCRT "Warning" or is a result of any assessment monitoring (includes closed system monitoring and inpatient pharmacy audits) will be reported in a narrative as in Table 23 [Metric 23].

During the current reporting period, instances of potential stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. A summary of the non-compliance activity is presented in Table 22.

Table 22 Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period: 29 October 2014 to 28 October 2015

Stakeholder[a]	Non-Compliance Activity	Non-Compliant Reason (categorized as reported by the stakeholder)	No. of events	No. of stakeholders
Non-Closed System Pharmacy	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF PMS that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Not aware of requirement to process cash claims	7	No. w/1 report: 7
		Received reject but dispensed drug	3	No. w/1 report: 3
		Dispensed drug without obtaining an authorization	1	No. w/1 report: 1
	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)	Altered prescription details for a REMS authorization	1	No. w/1 report: 1
		Total Non-Closed System Pharmacy Cases	**12**	
Prescriber	Prescriber failure to have a complete PPAF on file in a timely manner (5 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).	Not aware of PPAF requirement[b]	18	No. w/1 report: 18
		Completed PPAF with patient but failed to send PPAF to TIRF REMS	34	No. w/1 report: 34
		Aware of PPAF requirements but failed to complete PPAF[b]	9	No. w/1 report: 9
		No reason provided	21	No. w/1 report: 21
		Total Prescriber Reports	**82**	
		Total Number of Reports During This Reporting Period	**94**	

[a] There were no non-compliance cases for Wholesaler/Distributors or Closed-System Pharmacies.
[b] One Prescriber had two non-compliance events in two non-compliance categories.

During the reporting period, there were a total of 3 instances where TIRF prescriptions were dispensed by a non-closed system pharmacy (Table 22) that were written by non-enrolled prescribers after receiving a rejection from the TIRF REMS Access program [Metric 24].

1. On 23 October 2014, a pharmacy contacted the TIRF REMS Access program to troubleshoot a reject received due to a prescriber not being enrolled in the program. During the interaction with the TIRF REMS Access program, the pharmacy confirmed that drug was dispensed to the patient, despite receiving a reject. On 24 October 2014, the TIRF REMS Access non-compliance team contacted the pharmacy's authorized

representative and re-education was provided. The pharmacist confirmed that they understood that TIRF REMS drugs could not be dispensed without first obtaining a REMS authorization. On 11 November 2014, the TIRF REMS Access program issued a notice of non-compliance to the pharmacy. The TIRF REMS Access program made multiple attempts to reach the prescriber to assist with enrollment, but the prescriber did not respond.

2. On 14 April 2015, a pharmacy contacted the TIRF REMS Access program to inquire about assisting a prescriber with enrollment. During the interaction with the TIRF REMS Access program, the pharmacy confirmed that drug was dispensed to the patient on two separate occasions. The pharmacy advised that when they received a reject for the prescriber who wrote the prescription, the processed the prescription using an alternate enrolled prescriber from the same practice. On 20 April 2015, the TIRF REMS Access non-compliance team contacted the pharmacy's authorized representative and re-education was provided. The pharmacist advised they dispensed drug so that the patient would not be without treatment. The pharmacist confirmed that they understood that TIRF REMS drugs could not be dispensed without first obtaining a REMS authorization. On 24 April 2015, the TIRF REMS Access program issued a notice of non-compliance to the pharmacy. The TIRF REMS Access program contacted the prescriber to assist with enrollment, and on 14 April 2015 the prescriber successfully enrolled in the TIRF REMS Access program.
3. On 07 July 2015, a pharmacy contacted the TIRF REMS Access program to troubleshoot a reject received due to a prescriber not being enrolled in the program. During the interaction with the TIRF REMS Access program, the pharmacy confirmed that drug was dispensed to the patient, despite receiving a reject. On 13 July 2015, the TIRF REMS Access non-compliance team contacted the pharmacy's authorized representative and re-education was provided. The pharmacist advised they dispensed drug so that the patient would not be without treatment. The pharmacist confirmed that they understood that TIRF REMS drugs could not be dispensed without first obtaining a REMS authorization. On 21 July 2015, the TIRF REMS Access program issued a notice of non-compliance to the pharmacy. The TIRF REMS Access program contacted the prescriber to assist with enrollment, and on 17 July 2015 the prescriber advised he did not have time to enroll in a REMS program and stated he understood that he would be unable to prescriber TIRF medicines until enrollment was completed.

No additional compliance cases for these pharmacies have been identified as of the end of the reporting period.

There were no instances in which a prescription was dispensed by a non-enrolled pharmacy [Metric 25].

As shown in Table 22, there were 12 instances in which a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits [Metric 26].

No reports of TIRF medicines being prescribed to an opioid non-tolerant individual [Metric 27] or cases of inappropriate conversions between TIRF products [Metric 28] were received by sponsor companies during this reporting period.

Table 23 summarizes in narrative form all resolved non-compliance cases (n=6) and potential non-compliance events that remain pending as of the end of the reporting interval (n=1).

Table 23 Non-Compliance Reports in the Current Reporting Period: 29 October 2014 to 28 October 2015

Report Description (N=7)	Report Status	Mitigating Action
ID# 283 (Case # 13861174, 18918829 & 22270353) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 20 September 2013 for not submitting PPAFs for 5 patients. **[36-Month Assessment Report Non-Compliance]** Prescriber was issued a second Notice for Non-Compliance on 20 May 2014 for not submitting PPAFs for 6 patients. On 10 November 2014 the prescriber was again identified as not submitting PPAFs for 6 patients.	**Closed**	The TIRF REMS Access program re-educated the prescriber on 18 November 2014. The prescriber stated that the reason he has not submitted PPAFs is due to user error in completing the attestation electronic signature on the TIRF REMS website. The prescriber was reminded that the office will receive a confirmation from the website when a PPAF is submitted correctly and also provided directions on how to successfully complete and submit the PPAFs with the electronic signature. **[48-Month Assessment Report Update]** The prescriber was issued a Warning for Non-Compliance on 05 December 2014 requiring that a CAP be submitted by 30 December 2014. The prescriber submitted a CAP on 29 December 2014. The CAP was not approved as it did not align with the re-education provided to the prescriber; rather, the prescriber requested that the faxes and website be checked for the missing PPAFs. The prescriber stated that the forms were faxed because the prescriber had no success submitting forms on the website. A revised CAP was requested and received on 16 January 2015. Again, the CAP was not approved as it did not align with the re-education provided to the prescriber. The corrective action stated that the prescriber understood the guidelines/policies for prescribing TIRF medicines. A revised CAP was again requested and received on 17 February 2015. The corrective action stated that the prescriber and his staff were trained on how to submit PPAFs via fax and the website. This CAP was approved by the NCRT on 19 February 2015. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report Description (N=7)	Report Status	Mitigating Action
ID# 294 (Case # 20214924 & 22596663) On 11 June 2014 the prescriber was identified as not submitting PPAFs for 5 patients. The TIRF REMS Access program attempted to contact the prescriber multiple times between 12 June 2014 and 16 July 2014. A request for contact was issued to the prescriber after multiple unsuccessful contact attempts. The prescriber failed to contact the program for re-education by the deadline of 18 July 2014. A formal Notice of Non-Compliance was issued to the prescriber on 18 July 2014. None of the outstanding 5 PPAFs were submitted as all patients were identified as not continuing therapy. On 04 December 2014 the prescriber was again identified as not submitting PPAFs for 7 new patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access program attempted to contact the prescriber multiple times between 04 December 2014 and 30 December 2014. A request for contact was issued to the prescriber after multiple unsuccessful contact attempts. The prescriber failed to contact the program for re-education by the deadline of 21 January 2015. After no response to additional attempts to contact, a Warning letter was issued to the prescriber on 05 February 2015 requiring that a CAP is submitted by 26 February 2015. A CAP was received on 20 February 2015 stating that patients are seen at different locations and the signed PPAFs were misplaced. The prescriber stated that starting immediately PPAFs will be completed online. The NCRT approved the CAP on 11 February 2015. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
ID# 305 (Case # 12481943, 15791475, 21540583 & 23454251) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 12 March 2013 for not submitting PPAFs for 13 patients and a Warning letter requiring a CAP on 05 November 2013 for not submitting PPAFs for 11 patients. **[36-Month Assessment Report Non-Compliance]** The prescriber failed to submit a CAP by the deadline of 26 November 2013. To prevent patient access issues, the prescriber was granted an extension until 09 January 2014 by the NCRT as the prescriber was	**Closed**	The prescriber was contacted and re-educated on 17 February 2015. The prescriber stated that the patient count for the outstanding PPAFs is a small percentage of his patient population and he did not understand why this was considered non-compliance. The TIRF REMS Access program reminded the prescriber that he is responsible to submit PPAFs for every new patient prior to their first prescription. Due to the number and severity of offenses, the prescriber was suspended from the TIRF REMS Access program on 26 February 2015 and required to submit a new CAP within 10 business days. A CAP was received the same day. The NCRT did not approve the CAP as there were too limited of details provided to ensure the prescriber understands the requirements and will comply. A revised CAP was received on 02 March 2015 and approved by the NCRT on 03 March 2015. The non-compliance case was closed and the TIRF REMS Access program

Report Description (N=7)	Report Status	Mitigating Action
in the process of transitioning office practices. The prescriber failed to submit a CAP by the extended deadline and was suspended from the TIRF REMS Access program. A CAP was received on 14 January 2014 stating that the prescriber will ensure that PPAFs are submitted the same day as when the prescription is written or at least within the 10 day grace period. The CAP was approved by the NCRT on 15 January 2014 and the prescriber's suspension from the TIRF REMS Access program was removed. On 18 September 2014 the prescriber was again identified as not submitting PPAFs for 6 patients. The prescriber was issued a second Warning Letter on 20 October 2014 requiring a CAP be submitted by 10 November 2014. A CAP was received the same day and approved by the NCRT on 22 October 2014. **[48-Month Assessment Report Non-Compliance]** On 05 February 2015, the prescriber was again identified as not submitting PPAFs for 9 patients.		monitored the prescriber's adherence to PPAF activities for 30 days. In addition to monitoring, the CEO/Head of Practice at this prescriber's location was contacted and informed of the trend in non-compliance associated to this prescriber. PPAFs for all new patients were received within the grace period. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
ID# 314 (Case # 13861166, 18732022 & 23904486) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice for Non-Compliance on 13 August 2013 for not submitting PPAFs for 5 patients. **[36-Month Assessment Report Non-Compliance]** Prescriber was issued a second formal Notice for Non-Compliance on 09 April 2014 for not submitting PPAFs for 6 patients.	**Closed**	The prescriber was contacted and re-educated on 12 March 2015. The prescriber stated that he understands that it is his responsibility to ensure that PPAFs are submitted for each new patient prior to their first prescription. A first Warning letter was issued on 24 March 2015 requiring a CAP be submitted by 21 April 2015. A CAP was received on 08 April 2015. The NCRT did not approve the CAP as it did not address why the non-compliance occurred and the corrective action moving forward. A revised CAP was received on 23 April 2015. The NCRT did not approve the CAP as the prescriber needed to take responsibility for submitting PPAFs and not rely on his office staff to complete the PPAFs. A revised CAP was received on 06 May 2015 stating that the prescriber would personally fill out the PPAFs for new patients. This

Report Description (N=7)	Report Status	Mitigating Action
[48-Month Assessment Report Non-Compliance] On 03 March 2015, the prescriber was again identified as not submitting PPAFs for 5 patients.		CAP was approved by the NCRT. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
ID#357 (Case 12925438, 20277916, 25221416 #) **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a formal Notice for Non-Compliance on 07 May 2013 for not submitting PPAFs for 6 patients. **[36-Month Assessment Report Non-Compliance]** Prescriber was issued a second formal Notice for Non-Compliance on 26 June 2014 for not submitting PPAFs for 5 patients. **[48-Month Assessment Report Update]** On 04 June 2015 the prescriber was identified as not submitting PPAFs for 5 new patients who were at least 10 days past enrollment.	**Closed**	The prescriber was contacted by the TIRF REMS Access program and was re-educated on 08 July 2015. The prescriber stated that the reason for missing PPAFs was due to his busy practice location and his staff's difficulty in keeping up with paperwork. The prescriber confirmed he understood that it is his responsibility to ensure that PPAF's are completed and submitted. The prescriber submitted 4 of the 5 PPAFs. The last outstanding PPAF will not be submitted as it was for a patient identified as not continuing therapy. On 16 July 2015 the NCRT issued a first Warning letter with a request for a CAP by 06 August 2015. A CAP was received from the prescriber on 20 July 2015. After 2 attempts at prescriber outreach, on 27 July 2015, the prescriber's office staff was advised that due to lack of information provided in the CAP, it was not approved and should be revised and resubmitted. The prescriber provided a revised CAP with additional information on 04 August 2015. The prescriber stated that PPAF pads had been placed inside of every patient room and forms had been added to the front desk. Additionally, one senior staff member was placed in charge of faxing all forms to ensure that every form sent to the TIRF REMS Access program receives a fax confirmation. Forms would be sent once in the morning and once at the end of the day to ensure that they are all submitted to the TIRF REMS Access program. The NCRT approved the CAP on 12 August 2015 and this non-compliance case was closed. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report Description (N=7)	Report Status	Mitigating Action
ID#359 (Case # 20687552, 22901956, 25616311) On 18 July 2014, the prescriber was identified as not submitting PPAFs for 6 patients. On 18 July 2014 the prescriber was re-educated on the TIRF REMS Access program requirements. The prescriber stated that office staff handled completion of PPAFs and the reason the PPAFs had not been submitted was due to a change in his office locations. The prescriber confirmed he now understood that submission of PPAFs was his responsibility. On 24 July 2014, a formal Notice for Non-Compliance was issued to the prescriber. The prescriber submitted 5 of the 6 PPAFs. The last outstanding PPAF will not be submitted as it was for a patient identified as not continuing therapy. On 26 December 2014, the prescriber was again identified as not submitting PPAFs for 5 patients. On 21 January 2015, a request for contact correspondence was sent to the prescriber after multiple unsuccessful contact attempts between 02 January and 21 January 2015. The prescriber failed to contact the team for re-education by the deadline of 11 February 2015. A second formal Notice for Non-Compliance was issued to the prescriber on 20 February 2015. The prescriber submitted 3 of the 5 PPAFs. The last 2 outstanding PPAFs will not be submitted as they were for patients identified as not continuing therapy. On 02 July 2015, the prescriber was again identified as not submitting PPAFs for 5 patients who were at least 10 days past enrollment.	**Closed**	The TIRF REMS Access program re-educated the prescriber on 13 July 2015. The prescriber stated that his fax machine had not been working and most of his staff had changed since his last non-compliant event. The prescriber confirmed that he understood that it is his responsibility to complete and submit PPAFs for all patients. The prescriber submitted 1 of the 5 PPAFs. The last 4 outstanding PPAFs will not be submitted as they were for patients identified as not continuing therapy. A first Warning letter was issued on 27 July 2015 requiring a CAP by 17 August 2015. A CAP was received from the prescriber on 05 August 2015; however, it was unsigned by the prescriber. The prescriber stated that they had set up their electronic medical records to issue a message alert in a patient's file when any of the practitioners prescribed a TIRF medicine. When the medical assistant received a TIRF REMS prescription from the doctor to be input into the patient's electronic chart, the message would alert the staff to complete the PPAF during the patient's visit and send to the TIRF REMS Access program by end of business the same day. All staff had been educated on the policy change, effective 05 August 2015. The NCRT approved the CAP on 12 August 2015 pending prescriber signature. On 18 August 2015, a signed CAP was received from the prescriber and this non-compliance case was closed. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report Description (N=7)	Report Status	Mitigating Action
ID#380 (Case # 25444573, 26320577) On 22 June 2015, the prescriber was identified as not submitting PPAFs for 6 patients. On 06 July 2015, a request for contact correspondence was sent to the prescriber after multiple unsuccessful contact attempts between 22 June and 04 July 2015. The TIRF REMS Access program made an additional 6 outreach attempts following the issuance of the request for contact correspondence. On 03 August 2015 a formal Notice for Non-Compliance was issued to the prescriber, and the prescriber was re-educated. The 6 outstanding PPAFs will not be submitted as they were for patients identified as not continuing therapy. On 03 August 2015, the prescriber was again identified as not submitting PPAFs for 6 patients.	**Open**	On 18 September 2015, a request for contact correspondence was sent with a Prescriber Overview after multiple unsuccessful outreach attempts between 26 August and 11 September 2015. The prescriber failed to contact the TIRF REMS Access program for re-education by the deadline of 10 October 2015. The 6 outstanding PPAFs will not be submitted as they were for patients identified as not continuing therapy. A first Warning letter was issued on 26 October 2015 with a request for a CAP. On 02 November 2015, a CAP was received from the prescriber; however, on 12 November 2015, the NCRT did not approve the plan as it did not align with the re-education received by the prescriber. The NCRT is following up with the prescriber to obtain a valid CAP.

6.2 Audits

As part of non-compliance monitoring, TIRF REMS Access program pharmacies may be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

6.2.1 Closed System Pharmacy Audits [Metric 20]

The REMS Assessment Plan includes the following components for closed system pharmacy audits:

(1) Verification of training for all pharmacists dispensing TIRF products

(2) Numbers of prescription authorizations per closed system

(3) 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.

The first component of the closed system pharmacy audit requirement is accomplished through the enrollment process for closed system pharmacies. To become enrolled the authorized representatives must attest that all pharmacies dispensing TIRF products will be trained on the TIRF REMS Access program requirements. The second component is done through the closed system pharmacy prescription authorization process. Closed system pharmacists are required to validate the enrollment status of the prescriber and patient prior to dispensing a TIRF product by calling or faxing the prescription details to the TIRF REMS Access program. The TIRF REMS Access program maintains records of prescription details and the associated REMS authorization. Table 18 provides information on all prescription authorizations by closed system pharmacy.

The third and final component includes reconciliation between the closed system pharmacy's dispensing data and the TIRF REMS Access program's REMS authorizations. To conduct this reconciliation, the TIRF REMS Access program requests dispensing records from the closed system pharmacies and compares the dispensing records to REMS authorization data from the TIRF REMS Access program. After confirmation that the closed system pharmacy agrees to participate in the reconciliation, a formal written request for data is issued upon request to the authorized representative detailing the data to be provided and the deadline for submission. Specific data requested include:

- RX number for each prescription dispensed
- DEA number or NPI number of the facility that dispensed each prescription
- DEA number or NPI number of the prescriber that issued each prescription
- Date and time of each prescription transaction
- TIRF REMS Authorization code obtained for each prescription dispensed
- Due to the structure of some closed system pharmacy networks, the headquarters may be unable to provide data for all pharmacy locations as no central data repository is in existence; each pharmacy location maintains their own data. In these cases a random

sample of pharmacy locations was selected by the TIRF REMS Access program for participation.

- Findings from each investigation are reviewed with the NCRT and actions were taken in accordance with the Non-Compliance Protocol.

The CSP assessment metric required auditing of at least 3 randomly selected CSPs. The TRIG proactively included all closed-system pharmacies in the audit with a request to provide dispensing records from 01 April 2014 through 30 April 2015. As a result, there were 6 audits conducted during this 48-month monitoring reporting period and 2 closed system pharmacies (ID #361 and #376) were found to be non-compliant with the TIRF REMS Access program requirements. Based on the identification of non-compliance, a non-compliance case was opened for each of these 2 closed system pharmacies.

Below are the details of these 6 closed-system pharmacy audits. Table 24 summarizes the reconciliation of the dispensing data from each closed system pharmacy and the authorizations received from the TIRF REMS Access program during the course of the 6 audits.

Table 24 Closed System Pharmacy Audits

Audit ID Number	Date Closed System Monitoring Request for Data Sent	Date Dispensing Records Received[1]	Total Dispenses/Total Dispenses Not Authorized by the REMS	Non-Compliance Identified?
1 (ID#361)	09 June 2015	18 June 2015	76/53	Y
2 (ID#376)	21 May 2015	11 August[2]	27/15	Y
3 (ID#CS1)	21 March 2015	22 June 2015	239/0	N
4 (ID#CS2)	26 May 2015	08 June 2015[3]	0/0	N
5 (ID#CS4)	22 May 2015	01 July 2015	48/0	N
6 (ID#CS6)	21 May 2015	19 June 2015	9/0	N

[1] The date range for dispensing records received was 01 April 2014 through 30 April 2015.
[2] Additional data was requested after the initial receipt of dispensing records. This follow-up data were received on 30 September 2015.
[3] Pharmacy provided confirmation that no TIRF medicines were dispensed during the reporting period (01 April 2014-30 April 2015).

Additional details on the 2 closed pharmacy audits that identified non-compliance are identified below.

Closed System Pharmacy Audit 1: ID#361 (Case #25478537)

Request for Data

On 19 May 2015, the TIRF REMS Access program conducted outreach to request feedback on the closed system pharmacy process, and spoke with the Authorized Pharmacist (AP). The AP advised that all of the pharmacies were required to follow the TIRF REMS Access program guidelines; however, they do not have any requirements on how they document the authorization

numbers. The AP stated that every Pharmacist In Charge of an individual pharmacy has been trained on the program requirements. The AP requested the prescription authorization data from the TIRF REMS Access program so that he can match it to his pharmacy's data. On 09 June 2015 dispensing data for Department of Defense (DoD) locations were sent to the AP via email.

A formal closed system monitoring request for data was sent via email, with a response requested by 19 June 2015.

Investigation

Dispensing records were provided on 18 June 2015, and the TIRF REMS Access program began to reconcile the data. The dispensing records contained data from July 2014 through May 2015 and included 78 instances where a TIRF product had been dispensed during the monitoring period. The dispensing records provided were compared to authorization data from the TIRF REMS Access program and data discrepancies were found and showed that in 55 of the 78 occurrences drug was dispensed without obtaining an authorization. The TIRF REMS Access program conducted outreach to confirm that the DoD had provided 100% of their dispensing data, among all of their dispensing locations, to complete reconciliation.

On 08 July 2015, the AP confirmed that the pharmacy had provided 100% of their dispensing data, including military logistics unit (MLU) locations. The team continued to reconcile information received, ensuring that MLU locations were excluded from the data.*

Findings

On 17 July 2015, after excluding MLU locations, reconciliation of the data showed 76 instances of dispensing TIRF medicines during this monitoring period. In 53 of the 76 instances TIRF medicines were dispensed without obtaining an authorization.

Outcome

A formal Notice for Non-Compliance was issued on 23 July 2015. Re-education concluded on 09 September 2015 both verbally and via e-mail contact. On 06 November 2015, the CAP was received from the AP. The AP stated that he conducted education and training at 8 separate DoD locations (49 dispensing transactions) and 1 non-enrolled pharmacy (1 transaction) and provided copies of the *Closed System Pharmacy Overview*. The AP had contacted the Chiefs of Pharmacy and Medical Logistics and instructed to use documentation in the patient's Electronic Health Record instead of the Pharmacy Dispensing Profile. The procurement channels were blocked for 3 outpatient pharmacy locations representing the remaining 3 dispensing transactions. The plan was reviewed and approved by NCRT on 11 November 2015. As of the end of the reporting period, no additional non-compliance cases for the DoD have been identified.

**FDA issued a REMS communication to each of the TIRF Sponsors on 29 June 2012 stating that it had determined that TIRF medicines can continue to be distributed to DoD MLU locations without enrolling them in the REMS.*

Closed System Pharmacy Audit 2: ID#376 (Case #26141978)

Request for Data

On 21 May 2015, during a call with the Veteran's Administration (VA) to request feedback on the closed system pharmacy process, the VA Authorized Representative stated they do not have a process to record the TIRF approval number. Each individual pharmacy is responsible for training their staff and each site had been provided the TIRF REMS Access program Guidelines.

A formal request for data correspondence was issued to the VA on 21 May 2015, with a response requested by 21 June 2015.

Investigation

In the request for data of 27 February 2014, the VA Authorized Representative had advised that each VA site stores their own dispensing records (there is no central data storage) and they requested that the TIRF REMS Access program select a sample of sites to provide dispensing records. Therefore, on 04 June 2015, the TIRF REMS Access program provided 10 randomly selected and enrolled VA closed-system dispensing locations (accounting for 10% of the enrolled population for VA) to the VA for reconciliation.

After many attempts to seek status of the data request, the dispensing data were received by the team by 11 August 2015 and reconciled by the TIRF REMS Access program. The closed system pharmacy dispensing data showed that only 1 of the 10 locations had dispensing activity during the reporting period. The single location dispensed 13 instances of TIRF medications without authorization.

On 18 August 2015, the NCRT recommended selecting a larger population of enrolled VA locations to request additional dispensing data. On 20 August 2015, they further requested that the VA provide updated dispensing data for the 5 locations determined to have non-compliance activity during the 36-month assessment to determine if these sites continue to dispense without authorizations.

Findings

By 30 September 2015, data had been received from VA and reconciled by the TIRF REMS Access program. The closed system pharmacy dispensing data supported that 3 of the 5 additional locations had dispensing activity during the monitoring period. The 3 locations dispensed a total of 27 instances of TIRF medication. Two of the 3 locations each had 1 instance of dispensing without an authorization. The NCRT recommended issuing a second notice of non-compliance.

Outcome

A formal Notice for Non-Compliance was issued to the headquarters on 09 October 2015 and the notice was distributed to the pharmacy locations on 29 October 2015. Re-education occurred both verbally and via e-mail on the same date.

In response to the Non-Compliance Letter of 29 October 2015, 3 sites responded with a Corrective Action plan in November 2015 (2 sites by 12 November 2015 and 1 site by 16 November 2015).

For 1 site, the event occurred because there was no SOP for documenting the authorization number. An SOP was developed and implemented to ensure that all requirements of the TIRF REMS Access program are implemented. The SOP was in place since May 2015. Compliance with the SOP has been self-audited and self-auditing will continue in the future.

At Site 2, the event occurred because on 03 November 2014, a fentanyl lozenge prescription was dispensed because pharmacy staff involved was unaware of the REMS program. On 04 December 2014, new order for drug was issued; however, at the time, pharmacy staff who were aware of the REMS contacted the provider. As a result of intervention, the medical order for the fentanyl lozenge was discontinued and a new order for morphine 10mg/5mL was issued. In short, the provider decided to switch to another drug instead of enrolling in the REMS program. A number of corrective actions were put into place: the pharmacy staff involved was counseled by the supervisor. A sign was placed in the vault, indicating that TIRF medicines cannot be dispensed without verifying that the physician and the patient are enrolled in the REMS program and have the proper authorization from the TIRF REMS Access program. A mail message with specific instructions regarding the TIRF REMS Access program was sent to Pharmacy Staff. The TIRF REMS Access program internet address was included in the orderable item as follows (FDA REMS program. Verify before prescribing/dispensing. www.TIRFREMSAccess.com). The corrective actions have been in place since 29 October 2015, no additional events have occurred to assess if these actions were effective, and no further actions are pending implementation.

At Site 3: the event occurred because there was a change in staffing and management in January 2013. There was limited dispensing of the TIRF medicines and change in personnel, so the current staff had forgotten or were not aware of the requirements to obtain authorization prior to dispensing. A CAP was developed to educate pharmacy staff that included education requirements for all staff to complete the TIRF REMS Access Education program; a copy of their certificate of completion is to be added to their competency folder; the TIRF medicines will be marked on the shelf to remind staff to acquire the dispensing authorization number prior to filling; a pharmacy service SOP was written to include steps needed when processing and filling a TIRF medicines prescription; a review of the TIRF REMS Access program will be added to an annual competency review; and a bi-annual review will be completed to confirm compliance. The CAP has been in place since July 2015. Non-compliance prevention that is currently in place includes following the CAP, completion of the bi-annual internal audit, and annual review of the SOP.

All CAPs were approved on 14 December 2015. It should be noted that in the 36-month report, there were 39 instances where drug was dispensed via the closed system process of which 17 did not have REMS authorization prior to dispensing. There was a marked improvement in compliance this reporting period.

As of the end of the reporting period, no additional non-compliance cases for the VA have been identified.

6.2.2 Inpatient Hospital Pharmacy Audits [Metric 21]

Since submission of the 36-Month FDA Assessment Report, the TRIG developed an inpatient pharmacy questionnaire to conduct the required inpatient pharmacy audits.

The audit questionnaire invitation was faxed to Authorized Inpatient Pharmacists of pharmacies enrolled in the TIRF REMS Access program requesting their participation. Once the AP agreed to participate, they received the audit questionnaire to complete, which included 2 qualifying questions to determine eligibility to participate in the audit:

1. Is your pharmacy a hospital pharmacy? Yes/No
2. In the previous 12 months, has your hospital pharmacy dispensed TIRF medicine? Yes/No

If the answer was no to either of the qualifying questions, the pharmacy did not qualify for the audit. If they answered yes to both qualifying questions, they were asked to finalize the Audit Questionnaire by completing the following 3 questions:

1. Provide the number of units dispensed within <insert date range>. (See National Drug Code [NDC] list for a current listing of TIRF NDCs)

   _____units of use of TIRFs dispensed to patients.
2. Did all pharmacists who dispensed TIRF medicines complete training on the TIRF REMS Access program prior to dispensing these products? Yes/No
3. Do you have procedures in place such as order sets/protocols to assure compliance with the TIRF REMS program requirements? Yes/No. If yes, are you willing to provide examples of an order set or protocol?

All completed questionnaires were to be returned to the TIRF REMS Access program via fax or phone by the date specified on the audit invitation.

A total of 24 enrolled inpatient locations were solicited for participation in the audit. Four of the 24 pharmacies did not respond to the audit initiation and 2 pharmacies decided not to participate. The remaining 18 pharmacy locations agreed to participate and completed the qualifying questions associated with the audit questionnaire. Of the 18 pharmacies, 12 pharmacies answered no to at least one of the qualifying questions and were either not a hospital inpatient pharmacy facility or had not dispensed TIRFs in the previous 12 months. The remaining 6 qualified to participate in the audit, and proceeded with answering the 3 remaining audit questions.

Based on responses to the 3 audit questions, the 6 audited inpatient hospital pharmacies were evaluated compliant with the TIRF REMS Access program requirements. Therefore, the 6 audits were closed and no non-compliance cases were opened.

7 SAFETY SURVEILLANCE

7.1 Adverse Event Reporting [Metric 29]

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

7.2 TRIG Sponsor Adverse Event Data of Interest [Metric 30]

Based on the current Assessment Plan, TRIG has conducted an aggregate root cause analysis of all spontaneous adverse event reports of addiction, death, overdose, and pediatric exposure from

the TIRF Sponsors. Based on this requirement the TRIG Sponsor companies used a third party, UBC, to conduct this analysis. The sponsors identified the appropriate Medical Dictionary for Drug Regulatory Activities (MedDRA) codes to provide data including narratives or MedWatch forms which UBC summarized based on the FDA's request (see Appendix 12.2). Reports were reviewed and duplicates consolidated, when possible. Originally case reports were selected based on the specified Preferred Terms (PTs); upon UBC's review of the narrative information, some case reports did not meet the specified criteria and were excluded from the analysis. Additionally, literature reports and reports from Poison Centers were excluded.

Metrics of interest included: the number of event reports in each event category of interest (addiction, death, overdose, pediatric exposures); counts of adverse events related to inappropriate conversions between TIRF products; counts of adverse events related to accidental and unintentional exposures; and counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients.

In the 36-Month FDA Assessment Report Acknowledgement Letter, the FDA stated that none of the TRIG spontaneous adverse events included a root cause analysis as specified in the Assessment Plan and requested that a root cause analysis of adverse events be reported to the TRIG Sponsors in the 48-month assessment report. The analysis has been added and data tables now report the potential causality for each case if sufficient information was available to make a determination. If there was insufficient information available and the potential causality could not be determined, this was noted in the table.

The reporting period used for this analysis was 29 August 2014 to 28 August 2015 to allow sufficient time to complete this analysis.

There were 312 unique case reports that met the specified criteria. After a review of the 312 MedWatch Forms or narratives, no reports of inappropriate conversions between TIRF products were noted. None of the narratives indicated unintentional exposures, or non-opioid tolerance. There was one report of accidental exposure during the reporting period where a female was accidentally exposed to a TIRF medication by her neighbor who was prescribed a TIRF medicine for cancer pain.

7.3 Number of Adverse Events of Special Interest

The total number of cases of interest reported during this reporting period is presented in Table 25 below. Of the 312 cases, 291 (93.3%) had an outcome of death, 12 (3.8%) were reports of addiction, 6 (1.9%) were reports of overdose, and 4 (1.3%) were pediatric exposures.

Table 25 Number of Cases of Adverse Events of Special Interest

AEs of Interest	Number of Reports	Percentage[a]
Total Number of AEs of Interest	**312**	
Addiction	12	3.8%
Death	291	93.3%
Overdose	6	1.9%
Pediatric Exposure	4	1.3%

[a]Cases may have more than one adverse event of interest.

Table 26 shows the current reporting period rates for each of the adverse events of special interest per 100,000 prescriptions. The rates per 100,000 prescriptions included for 29 August 2013-28 August 2014 is provided as a reference for the rates provided in the 36-Month FDA Assessment Report.

Table 26 Rate of Adverse Events by Total Prescriptions

Adverse Events of Interest	Current Reporting Period (29AUG2014-28AUG2015)		Reported During Previous Reporting Period (29AUG2013-28AUG2014)	
	Number of Adverse Events	Adverse Event Rates per 100,000 Prescriptions (N=112,522)	Number of Adverse Events	Adverse Event Rates per 100,000 Prescriptions (N=94,464)
Addiction	12	10.66	4	4.23
Death	291	258.62	362	383.21
Overdose	6	5.33	0	0
Pediatric Exposure	4	3.55	2	2.12

Table 27 shows the current reporting period rates for each of the adverse events of special interest per 100,000 population. The rates per 100,000 patients included for 29 August 2013-28 August 2014 is provided as a reference for the rates provided in the 36-Month FDA Assessment Report.

Table 27 Rate of Adverse Events by Total Patients

Adverse Events of Interest	Current Reporting Period (29AUG2014-28AUG2015)		Reported During Previous Reporting Period (29AUG2013-28AUG2014)	
	Number of Adverse Events	Adverse Event Rates per 100,000 Patients (N=15,922)	Number of Adverse Events	Adverse Event Rates per 100,000 Patients (N=14,772)
Addiction	12	75.37	4	27.08
Death	291	1827.66	362	2450.58
Overdose	6	37.68	0	0
Pediatric Exposure	4	25.12	2	13.54

Twelve (12) cases were classified as cases of addiction. Of the 12 cases, 3 had an outcome of "not recovered/not resolved" at the time of the cut off (28 August 2015); 1 had an outcome of "resolved"; and 7 had an outcome of "unknown." One patient experienced multiple events with different event outcomes of ongoing, recovered/resolved, and unknown (case outcome listed as ongoing). Table 28 provides details of these 12 cases. None of the 12 cases provided sufficient detail to perform a root cause analysis.

Table 28 Cases of Addiction Received from TRIG Sponsors during the Reporting Period: 29 August 2014 - 28 August 2015

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[1]**
1495	48	Female	24SEP2014, Unknown	26SEP2014	Drug withdrawal syndrome, Off label use	Off label use, pain	Unknown	None reported	None reported	Recovered/ Resolved	Insufficient Information
1512	UNK	Male	Unknown	14OCT2014	Drug dependence	Unknown	Unknown	None reported	None reported	Unknown	Possibly related
1544	UNK	Female	Unknown	21NOV2014	Drug abuse	Unknown	UNK	None reported	None reported	Unknown	Possibly related
1545	UNK	Male	Unknown	21NOV2014	Drug abuse	Unknown	UNK	None reported	None reported	Unknown	Insufficient information
1603	60	Female	DEC2014, 18DEC2014, DEC2014, NOV2014, Unknown, Unknown, Unknown, Unknown, Unknown, Unknown, Unknown	26FEB2015	Staphylococcal infection, Drug withdrawal syndrome, Suicidal ideation, Retching, Constipation, Dependence, Drug effect decreased, Hyposmia, Incorrect drug administration duration, Intentional product use issue, Nausea	Surgery, gastrointestinal disorder, surgery, gastrointestinal disorder, osteoporosis	Unknown	Gabapentin, Vancomycin, Phenergan, Evista	Fentanyl Transdermal System	Ongoing	Related
1665	59	Female	07APR2015, Unknown, Unknown, Unknown, Unknown, Unknown, Unknown	11MAY2015	Off label use, Arthralgia, Drug ineffective, Drug withdrawal syndrome, Gait disturbance, Musculoskeletal pain	Neck pain, back pain	2015-04-07 - UNK	Valium	Morphine	Not Recovered/ Not Resolved	Possibly related
1666	UNK	Female	NOV2014, Unknown, Unknown, Unknown	12MAY2015	Weight decreased, Drug effect incomplete, Drug withdrawal syndrome, Product quality issue	Cancer pain, breakthrough cancer pain	2014 - UNK	Hydromorphone	None reported	Unknown	Possibly related

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[1]**
1713	68	Female	Unknown	05AUG2015	Drug dependence, Intentional product misuse	Pain from cancer radiation treatments	Unknown	Oxycontin	None reported	Not Recovered/ Not Resolved	Not related
1738	UNK	Male	OCT2014, OCT2014, Unknown	30OCT2014	Constipation, Intentional drug misuse, Off label use	Arthritis	Unknown	None reported	Oxycodone	Not Recovered/ Not Resolved	Possibly related
1774	UNK	Male	Unknown	10MAR2015	Drug dependence, Drug ineffective, Loss of consciousness, Off label use, Product quality issue	Chronic back pain	2013-10 - UNK	None reported	Fentanyl Patches	Unknown	Possibly related
1802	UNK	Female	DEC2013, Unknown	21MAY2015	Drug dependence, Off label use	Pain	2013-12 - UNK	Celexa, Fentanyl Patch	None reported	Unknown	Possibly related
1827	UNK	Male	Unknown	25AUG2015	Depression, Drug dependence, Drug withdrawal syndrome, Therapy cessation	Unknown	Unknown	None reported	None reported	Unknown	Possibly related

[1] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.

UNK = Unknown

As a result of this review, 291 reports of death were noted. Sixteen of these 291 reported deaths were identified through the TIRF REMS Access program's PPAF renewal/follow-up process. A total of 172 reports of death without any other adverse event were reported. Of these 172 cases, 166 cases did not include enough information (e.g., indication for use, patient medical history, dates of use of the TIRF medication, and/or concomitant medications) to allow for an assessment of causality. In 6 cases, the cause of death was reported as related to an underlying cancer, and in 1 case, follow up information revealed that the patient was prescribed a TIRF medication, but never took the medication.

Of the 119 death case reports, 78 reports were due to neoplasm progression where death was attributed to cancer and 14 reports with an outcome of death were attributed to an underlying medical condition; two reports with death as an outcome were reported as disease progression both involving patients with cancer; one was due to an apparent suicide. However, the report also noted that patient had a medical history that included Stage IV esophageal cancer. There was one report of an accidental death involving a patient taking a TIRF medicine for pain who died in a house fire, and one report of drug toxicity that was accidental after TIRF medicine ingestion and anesthesia.

There were 7 cases with death as an outcome and off-label use as the Preferred Term but none were considered related to a TIRF product (6 reported an unknown cause and 1 reported a "natural" cause). There was one overdose that resulted in death involving a patient's daughter using the patient's TIRF product and oral opioids.

The last 14 reports of death included 4 reports of heart attack, cardiac arrest, or a heart disorder, 1 report of heart failure, 3 reports where a patient had a diagnosis of metastatic cancer and the death was not related to a TIRF medication, 1 death due to COPD, 1 death due to hepatic failure, 1 death due to septic shock due to cholecystitis. Three deaths were due to unknown causes.

A full line listing of deaths is presented in Appendix 12.3.

There were 6 overdose cases reported during this reporting period (Table 29). One case had an outcome of death with causality reported as possibly related. This case also appears in the death listing (Appendix 12.3). The remaining 5 cases included: 1 case with an unknown outcome, 2 cases with an outcome of recovered/resolved at the time of this report and 2 cases with an outcome of not recovered/not resolved. Five of the 6 cases did not provide sufficient detail to perform a root cause analysis. The final case with an outcome of death had a causality assessment of possibly related and was referenced above.

Table 29 Cases of Overdose Received from TRIG Sponsors during the Reporting Period: 29 August 2014 - 28 August 2015

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[1]**
1533	38	Female	05NOV2014, OCT2014, 2014, 2014, 2014, 2014	10NOV2014	Streptococcal infection, Sepsis, Drug tolerance, Overdose, Product quality issue, Underdose	Addison's disease, off label use, fibromyalgia, osteoporosis	2014-03 – UNK	None reported	None reported	Not Recovered/ Not Resolved,	Related
1540	UNK	Male	Unknown	19NOV2014	Accidental overdose, Apparent death, Dental implantation, Dental prosthesis user, Intentional product use issue, Mechanical ventilation, Tooth loss	Pain relief after cervical surgeries	Unknown	None reported	None reported	Not Recovered/ Not Resolved	Possibly related
1600	UNK	Unknown	01OCT2014, 01OCT2014, 01OCT2014	24FEB2015	Breakthrough pain, Overdose, Respiratory depression	Cancer pain	Unknown	None reported	None reported	Recovered/ Resolved	Possibly related
1625	56	Female	22MAR2015, MAR2015, MAR2015, MAR2015, MAR2015, MAR2015, FEB2015	23MAR2015	Overdose, Abdominal pain upper, Diarrhoea, Drug withdrawal syndrome, Rhinorrhoea, Vomiting, Yawning, Drug dispensing error	Complex regional pain syndrome, off label use	2015-03-22 - 2015-03-21	Amitiza, Armour Thyroid, Estradiol Testosterone, Fentanyl, Healthy Hair Skin and Nails B Complex/ Biotin, Lisinopril, Omeprazole, Potassium Chlor-Er, Progesterone, Vitamin D Cap D2 Ergo Calcifier	None reported	Recovered/ Resolved	Related

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[1]**
1668	UNK	Female	Unknown	13MAY2015	Overdose	Cancer pain	Unknown	None reported	Fentanyl Patch	Unknown	Insufficient information
1795[2]	UNK	Female	Unknown	07MAY2015	Overdose	Unknown	Unknown	None reported	None reported	Death	Possibly related

[1] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
[2] Patient 1795 is also described in the table for death found in Appendix 12.3.
UNK = unknown.

There were 4 pediatric cases reported during this reporting period (Table 30). No case had an outcome of death and 3 cases had an outcome of unknown at the time of this report.

In 3 of the 4 reports, the medication was intentionally prescribed to the pediatric patient. The fourth report had insufficient information to determine if the pediatric patient took the TIRF medicine.

No further details were obtained despite extensive follow-up attempts.

Table 30 Cases of Pediatric Exposures Received from TRIG Sponsors during the Reporting Period: 29 August 2014 - 28 August 2015

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[1]**
1474	15	Female	Unknown	29AUG2014	Drug administered to patient of inappropriate age	Unknown	Unknown	None reported	None reported	Unknown	Insufficient information
1478	15	Female	Unknown	03SEP2014	Drug administered to patient of inappropriate age	Unknown	Unknown	None reported	None reported	Unknown	Pediatric exposure resulting from off-label prescribing
1553	9	Male	Unknown	12DEC2014	Drug administered to patient of inappropriate age, Product use issue	Chronic pancreatitis	Unknown	Dilaudid, Percocet, Clonazepam	None reported	Unknown	Pediatric exposure resulting from off-label prescribing
1586	UNK	Male	Unknown	30JAN2015	Drug administered to patient of inappropriate age	Unknown	2014-03 - UNK	None reported	None reported	Not Recovered/ Not Resolved	Pediatric exposure resulting from off-label prescribing

[1] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.

UNK = unknown.

7.4 TIRF Product Surveillance Data [Metric 31]

7.4.1 Background

Surveillance data focusing on events of abuse, misuse, and death were evaluated using data from the RADARS System for the time period July 2010 to June 2015. Based on FDA request, the data included in this report compare event rates for a time period prior to full implementation of the TIRF REMS and a time period after REMS implementation. Additional updates to the RADARS System data analysis were made based on FDA feedback provided in the 36-Month FDA assessment report Acknowledgement Letter. Specific responses to each FDA request can be found in Appendix 12.4.

Data from five programs that gather data from unique populations along the spectrum of drug abuse were used to monitor for the non-medical use (abuse and misuse) of TIRF products. The data sources and the specific events evaluated in each are shown in Table 31 below.

Table 31 RADARS System: Data Sources and Specific Events

Data Source	Abuse	Intentional Misuse	Unintentional Therapeutic Errors	Unintended General Exposures	Emergency Department Visits & Hospitalizations	Deaths	Major Medical Outcomes and Deaths[e]
1. Poison Center Program	✔ [a]	✔	✔	✔	✔	✔	✔
Treatment Center Programs							
2. Opioid Treatment Programs	✔ [b]						
3. Key Informants Survey	✔ [b]						
4. College Survey	✔ [c]						
5. Impaired Health Care Workers Program	✔ [d]						

[a] Abuse defined as exposure resulting from intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect

[b] Abuse defined as a respondent endorsing the use of a product to get high in the past 30 days

[c] Abuse defined as endorsement of a non-medical use of a drug in the past 90 days

[d] All reported cases are considered abuse; data may include a small fraction of drug diversion information.

[e] This column includes the events included in the column titled “deaths” as well as major medical outcomes that did not lead to death

Trends over time for the TIRF products were compared to 3 comparator groups that are not directly impacted by the TIRF REMS to determine how the trend in TIRF rates compares to the secular trend in other opioids. The comparators used in this report were:

- Schedule II IR opioids
- Schedule II opioids
- Schedule II opioids excluding methadone

Recently, IR hydrocodone was changed from a Schedule III opioid to a Schedule II opioid. As IR hydrocodone was not included in the group of Schedule II opioids in previous reports and was not a Schedule II drug for the entire study period, data were analyzed two ways. The primary analyses were conducted without IR hydrocodone in the Schedule II IR opioid group. Sensitivity analyses were then conducted as if IR hydrocodone was a Schedule II IR opioid for all quarters.

Data from IMS Health are used to estimate total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP-code level for all TIRF REMS opioids and comparator groups. Totals of prescriptions and dosing units in the three digit zip codes covered by the RADARS System Programs were computed and used as the denominators when calculating product availability rates. IMS data does not capture methadone dispensed through opioid treatment programs (OTPs), thus the count of methadone prescriptions is an undercount. Prescription rates will be scaled per 10,000 prescriptions and dosing rates will be scaled per 100,000.

Rates of abuse, misuse, overdose, unintentional therapeutic errors, unintentional general exposures, emergency department visits/hospitalizations, deaths, and major medical outcomes were calculated using the 2010 US decennial census estimated from the three-digit zip codes covered in the RADARS System Programs as the denominator. Population rates will be scaled per 100,000 population.

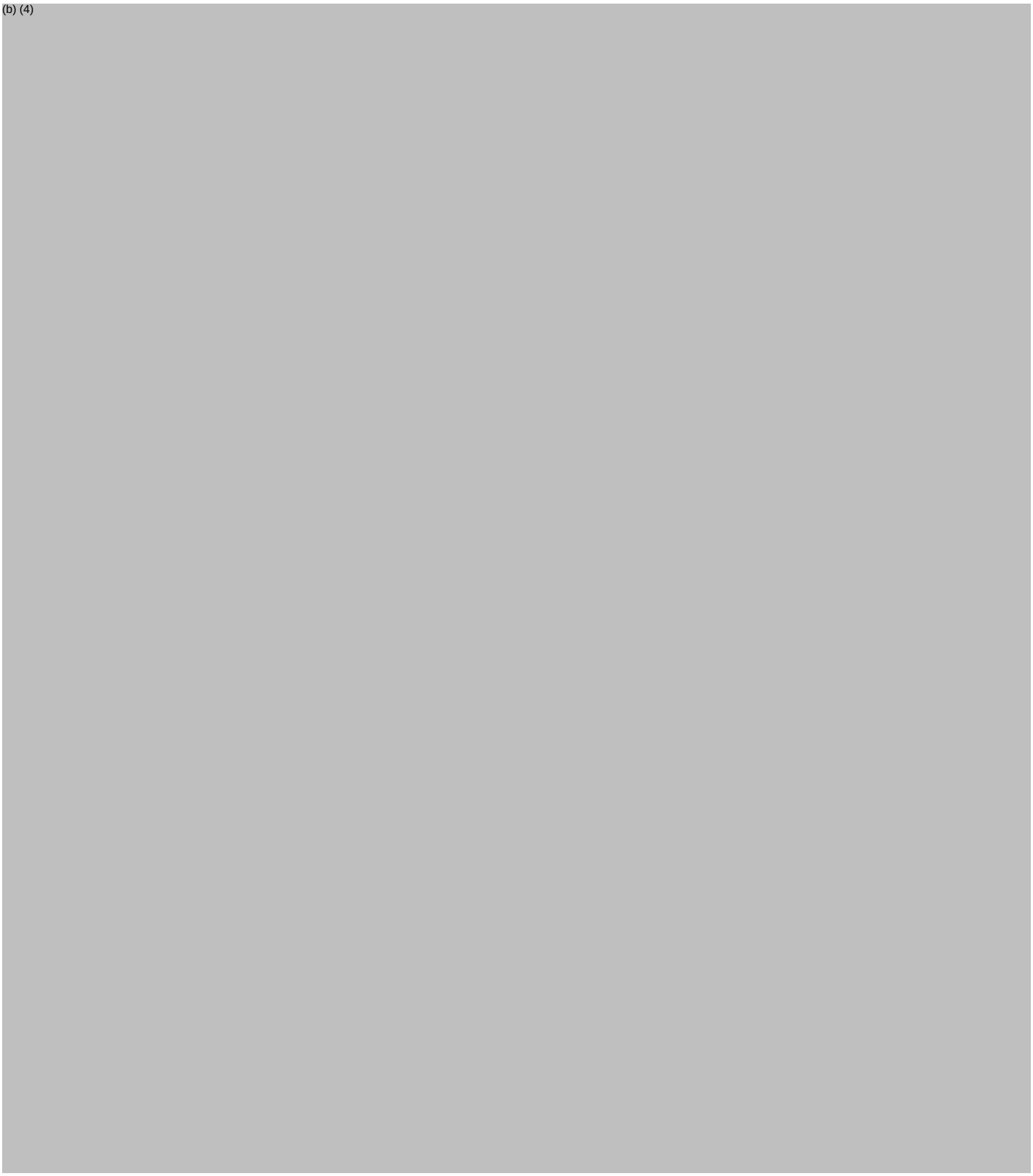
Additional details regarding the data sources and specific events can be found in the RADARS System Report Protocol (Appendix 12.5).

7.4.2 RADARS Results

This RADARS System Report summary presents the results of an analyses of the effectiveness of the TIRF REMS drawn from 5 data sources (i.e., Poison Center Program, Treatment Center Programs combined [includes OTP survey and SKIP], College Survey, and Impaired Healthcare Workers Program). The full report from the RADARS System Program is included as Appendix 12.6.

(b) (4)

(b) (4)



(b) (4)

Table 32 Summary of RADARS Findings by Program, Outcome, and Denominator

Program	Outcome	Denominator	Drug group	Percentage change	Interaction
Poison Center Program	Intentional abuse exposure	Population	TIRF Products	(b) (4)	
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Intentional misuse exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Unintentional therapeutic error	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		

Program	Outcome	Denominator	Drug group	Percentage change (95% CI)	Interaction p-value
			Schedule II Opioids Excluding Methadone	(b) (4)	
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Unintentional general exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Emergency department visits/hospitalization exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		

Program	Outcome	Denominator	Drug group	Percentage change (95% CI)	Interaction p-value
			Schedule II Opioids Excluding Methadone	(b) (4)	
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Major medical outcomes and death exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
Treatment Center Programs Combined	Past 30 day use to get high	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		

Program	Outcome	Denominator	Drug group	Percentage change (95% CI)	Interaction p-value
			Schedule II Opioids Excluding Methadone	(b) (4)	
College Survey Program	Past 3 month nonmedical use	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
Impaired Health Care Worker Program	Abuse	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		

8 PERIODIC SURVEYS OF STAKEHOLDERS

Surveys were conducted to assess patients'/caregivers', pharmacists', and prescribers' KAB regarding the safe use of TIRF medicines as described in the educational materials for all stakeholders, enrollment form (pharmacists and prescribers only), Full Prescribing Information (pharmacists and prescribers only) and medication guides (prescribers and patients) for each product, and the PPAF (prescribers and patients only). The survey protocols describe the administration of the individual surveys that were conducted among patients who are treated with TIRF medicines or their caregivers, prescribers, and pharmacists; the survey KAB reports include summarization of all data collected during the survey (see Appendix 12.7.1, 12.7.2, and 12.7.3, respectively, for the patient, pharmacist, and prescriber KAB reports which include the protocol and survey). Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

8.1 Key Risk Messages

The questions and statements within the KAB surveys for patients/caregivers, pharmacists, and prescribers were constructed to test the stakeholders' understanding of the key risk messages of the REMS. The TRIG established a desired threshold of 65%. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message. The purpose of this threshold was to assist TRIG in tracking and monitoring the data for each key risk message across each wave ultimately providing direction in determining which area(s) would require improvement to ensure the patient/caregiver, pharmacist, and prescriber KAB surveys were meeting the goals of the REMS.

8.2 Patient KAB Survey

The patient survey launched on 24 July 2015 and closed on 03 September 2015. Feedback from FDA was provided in the 36-month Assessment Report Acknowledgement Letter and where applicable these changes were implemented in the 48-month survey. Changes included removing 'Onsolis' as a response option throughout the survey because it is no longer available, moving specified existing survey questions under key risk messages, and including an analysis of demographics of the patient survey respondents compared to the demographics of patients receiving a TIRF product.

The specific goals of the TIRF medicines patient/caregiver KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients/caregivers regarding TIRF medicines. The focus of the survey included the following: 1) TIRF medicines can cause life-threatening breathing problems that can lead to death, patients should take TIRF medicines only if they are opioid-tolerant, and patients should strictly follow the directions of the HCP, 2) patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to an HCP, 3) patients should not give TIRF medicines to anyone else even if they have the same symptoms, and 4) TIRF medicines should be stored in a safe place away from children and properly disposed. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the PPAF.

Invitations (and reminders) were sent to all known patients/caregivers who had filled a prescription within the 4 months (120 days) prior to survey launch. From the total of 432 patients/caregivers who accessed the survey, 314 (72.7%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (98.7%) completed the survey, exceeding the target of 300 completed surveys. The geographic distribution of survey respondents was similar to the general population of TIRF users (comparison requested by FDA).

In general, there is an overall trend across all patient/caregiver KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward maintenance or improvement in patient/caregiver knowledge and understanding of the key risk messages. Of the 19 components included as part of the 6 key risk messages, 13 components had a response rate >80%, and 3 components had a correct response rate between 67.7% and 74.8%. The remaining 3 components within key risk messages 2 and 3 had a correct response rate which fell below the desired threshold of 65%. Patients scored consistently low on two of 19 components across all survey waves which included 1) *TIRF medicines should not be taken for long-lasting pain not from cancer, like arthritis joint pain* (43.9% correct) and 2) *a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine* (39.4% correct). In addition, revising one question (TIRF medicines should only be taken by patients who are opioid tolerant) to be specific to *'cancer'* patients, resulted in a large decrease in the correct response rate from the previous survey (85.2% to 43.5%), which may indicate that some respondents were receiving TIRF medicine for a non-cancer associated indications.

For complete data and results see Appendix 12.7.1.

8.3 Pharmacy KAB Survey

The pharmacy survey launched on 31 August 2015 and closed on 16 September 2015. Feedback from FDA was provided in the 24-month and 36-month Assessment Report Acknowledgement Letters and where applicable these changes were implemented in the 48-month survey. Changes included steps to include a higher percentage of non-supervisory dispensing pharmacists participate in the survey, adding questions addressing CYP3A4 interactions with TIRF medicines and that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid, removing 'Onsolis' as a response option throughout the survey because it is no longer available, and moving specified existing survey questions under key risk messages.

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients. The survey also included questions about whether pharmacists received, read, understood, and used the product-specific educational materials, and included questions about compliance with the REMS requirements.

Invitations (and reminders) were sent to a random sample of pharmacies enrolled in the TIRF REMS Access program as of 30 June 2015, and were distributed to pharmacists who dispense TIRF products and were known to have received the REMS educational materials. From the total of 607 pharmacists who accessed the survey, 334 (55.0%) pharmacists met eligibility criteria, and of those who met eligibility criteria, 301 (90.1%) completed the survey, exceeding the target of 300 completed surveys.

In general, there is an overall trend across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in pharmacist knowledge and understanding of the key risk messages. Of the 29 components included as part of the 4 key risk messages, 20 components of the key risk messages had a response rate >80%, and 7 components had a response rate between 65.1% to 78.7%. Two components within the key risk messages had a correct response rate below the desired threshold of 65% (Component 6c and Component 9e). The correct response rate for Component 6c (*A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 41.9%. This component was added to the 48-month survey based on feedback provided by FDA in the 24-month and the 36-month FDA REMS Acknowledgement Letter. Correct response rate for Component 9e (*Chronic non-cancer pain* is not an indication for which TIRF medicines can be prescribed) was 50.8% for this 48-month survey. Component 9e has had a low correct response rate across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). The survey score for Component 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

For complete data and results see Appendix 12.7.2.

8.4 Prescriber KAB Survey

The prescriber survey launched on 31 August 2015 and closed on 16 October 2015. Feedback from FDA was provided in the 24-month and 36-month Assessment Report Acknowledgement Letter and where applicable these changes were implemented in the 48-month survey. Changes included adding questions on whether the respondent works in a closed system, and for respondents who stated they prescribe TIRF medicines for chronic non-cancer pain addressing why they feel that this is an appropriate use of TIRF medicines, removing 'Onsolis' as a response option throughout the survey because it is no longer available, moving specified existing survey questions under key risk messages, removing Question 19 (*Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?*), and including an analysis of demographics of the prescriber survey respondents compared to the demographics of the general population of TIRF prescribers.

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed. The survey also included questions about whether prescribers received, read, understood, and used the product-specific educational materials, and included questions about compliance with the REMS requirements.

Invitations (and reminders) were sent to a random sample of prescribers who prescribed TIRF products, were known to have received the REMS educational materials, and who were enrolled in the TIRF REMS Access program as of 30 June 2015. From the total of 587 respondents who accessed the survey, 350 (59.6%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (88.6%) completed the survey, exceeding the target of 300 completed surveys. The geographic distribution of survey respondents was similar to the overall population of prescribers who prescribe TIRF medicines (comparison requested by FDA).

In general, there is an overall trend across all prescriber KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in prescriber knowledge and understanding of the key risk messages. Of the 31 components included as part of the 4 key risk messages, 21 components of the key risk messages had a correct response rate >80% and 9 components had a correct response rate between 67.7% and 78.7%. For Component 9e, 201 prescribers (64.8%) indicated they do not prescribe TIRF medicines for chronic non-cancer pain. The 34.2% of prescribers who stated they do prescribe TIRF medicines for chronic non-cancer pain were presented with 2 additional questions as requested by the FDA; the type of chronic pain conditions they prescribe a TIRF medicine to treat, and the reasons for selecting a TIRF medicine to treat these conditions. Based on prescriber responses, and the high percentage of respondents who indicated they received and read the REMS educational materials, the responses may reflect behavior more than knowledge. That is, prescribers are aware of the labeled indication but choose to prescribe off-label for certain patients.

For complete data and results see Appendix 12.7.3.

8.5 Overall Conclusion for KAB Results

The consistently high level of stakeholder understanding of key risk messages in the 48-month surveys indicates that the goals of the TIRF REMS are being met with existing tools. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

9 FDA COMMUNICATIONS

REMS Modification 3 was approved by FDA on 24 December 2014. All metrics included in the revised and approved assessment plan have been incorporated into this 48-Month FDA Assessment Report. Post-submission of the 36-Month FDA Assessment Report, TRIG responded to 4 information requests and provided a response to the 36-Month FDA Assessment Report Acknowledgement Letter. Per agreement with FDA a consolidated Drug Master File (DMF) submission was made on 12 October 2015, to include all correspondence related to the 36-Month FDA Assessment Report.

Within the Acknowledgement Letter FDA made 3 requests that, based on timing for receipt of the communication, could not be included in this assessment report. As acknowledged by FDA on 13 November 2015, the TRIG plans to submit a Supplemental Report with 2 of these requests with an estimated submission date of 04 May 2016. As discussed in Section 4, the remaining request for outreach to prescribers and pharmacies that did not re-enroll is unwarranted as no barrier to patient access has been observed.

10 POST-APPROVAL STUDIES AND CLINICAL TRIALS

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

11 DISCUSSION

The TIRF REMS Access program was approved on 28 December 2011 and successfully launched on 12 March 2012, approximately 11 weeks after approval. This 48-month assessment report covers the timeframe between 29 October 2014 and 28 October 2015.

REMS enrollment continues to increase, with 2,340 new prescribers (Section 5.1.2), 5,892 new pharmacies (Section 5.1.3), and 3 new distributor(s) (Section 5.1.4) enrolled in this reporting period. A total of 152,686 prescriptions were submitted for approval during this reporting period, and 143,763 (94.2%) prescriptions encountered no REMS-related rejections prior to being authorized (Section 5.1.5). These data plus the ongoing stakeholder re-enrollment activity indicate that the program does not present a significant barrier to accessing these important medications while continuing to meet the safety goals of the REMS.

Prescription dispensing outside the established PPAF requirements was nearly eliminated as a result of the corrective actions implemented during the previous reporting period to significantly reduce this occurrence (Section 5.1.6). In this 48-month report there was only one prescription for one patient dispensed beyond 10 days after patient enrollment compared with 6 prescriptions for one patient in the 36-month report. The TIRF REMS Access program continues to monitor the electronic systems and stakeholder reports for issues and, where appropriate, corrective actions or system improvements are instituted.

During the current reporting period, 101 confirmed instances of stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. This included 89 prescriber reports and 12 non-closed system pharmacy reports (a total of 94 cases presented in Table 22 and 7 narratives included in Table 23). Of the cases presented by non-compliance scenario (Table 22), a decrease was seen in the number of confirmed instances of non-compliance between the 36-Month Assessment Report and this reporting period for inpatient pharmacy dispenses for outpatient use (1 vs. 0 reports), submission of a claim that did not go through REMS edits (14 vs. 12 reports), dispensing prescriptions outside of the closed system authorization process (7 vs. 0), and prescriber failure to have a complete PPAF on file in a timely manner (120 vs. 82 reports). There were no wholesaler/distributor or closed system pharmacy reports during this reporting period (Section 6.1) as opposed to one report during the last reporting period.

Audits of 6 closed system pharmacy entities were conducted during this reporting period. Two closed system entities were found to be non-compliant with the TIRF REMS Access program requirements. These pharmacies were re-educated, issued a notice through the NCRT and submitted a CAP which was approved by the NCRT. All cases have been closed (Section 6.2). A decrease was seen in the number of instances where a REMS authorization was not received prior to dispensing a TIRF product between the 36-Month Assessment Report and the current reporting period (513 vs. 68 instances).

Since submission of the 36-Month FDA Assessment Report, the TRIG developed and implemented an inpatient pharmacy questionnaire to conduct the required inpatient pharmacy audits. Audits of 6 inpatient pharmacies were conducted during this reporting period and no non-compliance was identified for any inpatient pharmacy.

(b) (4)

The analysis of spontaneous reports of adverse events of interest used aggregated data from TRIG sponsors with currently marketed products. There were 312 unique case reports that met the specified criteria for addiction (n=12), overdose (n=6), death (n=291), and pediatric exposures (n=4). After a review of the associated MedWatch Forms or narratives for root cause analysis, no reports of inappropriate conversions between TIRF products were noted. Additionally, only one of the narratives indicated accidental, unintentional exposures and there were no cases of use by non-opioid tolerant patients. There was one report of accidental exposure with an outcome of recovered/resolved during the reporting period. There were 4 reports of pediatric exposure (Section 7). In 3 of the 4 reports, the medication was intentionally prescribed to the pediatric patient. The fourth report had insufficient information to determine if the pediatric patient took the TIRF medicine.

The REMS goal of educating prescribers and pharmacists on the potential for misuse, abuse, addiction, and overdose is being documented through the completion of the Knowledge Assessment, which is required for enrollment. Effectiveness of the educational program is evaluated through the pharmacy and prescriber KAB surveys that are performed prior to each assessment report. Results of the 48-month surveys indicate a high level of understanding of safe use of TIRF medicines by pharmacists and prescribers. Key risk messages that are important for these stakeholders to understand include the fact that TIRF medicines are contraindicated in opioid non-tolerant patients, are only indicated for the management of breakthrough pain in adult cancer patients, contain fentanyl with abuse liability similar to other opioid analgesics, and are not interchangeable with each other on a mcg-to-mcg basis regardless of route of administration. Two exceptions where pharmacists scored low included understanding that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (41.9% correct), and that TIRF medicines are not indicated for chronic non-cancer pain (50.8% correct), which may indicate that some respondents are dispensing TIRF medicines for non-cancer-associated indications. For prescribers, 34.2% stated they do prescribe TIRF medicines for chronic non-cancer pain. Based on prescriber responses of the type of chronic pain conditions for which they prescribe and the reasons for selecting a TIRF medicine to treat these conditions, coupled with the high percentage of respondents who indicated they received and read the REMS educational materials, the responses may reflect behavior more than knowledge. That is, prescribers are aware of the labeled indication but choose to prescribe off-label for certain patients.

In general, there is an overall trend across all pharmacist and prescriber KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in pharmacist and prescriber knowledge and understanding of the key risk messages. Due to the high level of understanding of these concepts by pharmacists and prescribers, no modifications to

the educational program or Knowledge Assessment are recommended at this time (Sections 8.3 and 8.4, respectively).

Patient education is completed through HCP counseling and completion of a PPAF. The patient KAB survey results indicate that the patient-oriented educational materials including the PPAF and Medication Guide for each product are effective tools at communicating safe use messages to patients, including the importance of not sharing TIRF medicines, taking TIRF medicines as prescribed, and properly disposing unused TIRF medicines. In general, there is an overall trend over time (12-month, 24-month, 36-month, and 48-month surveys) toward maintenance or improvement in patient knowledge and understanding of the key risk messages. Patients scored consistently low on 2 of 19 components: 1) that TIRF medicines should not be taken for long-lasting pain not from cancer (43.9% correct), like arthritis joint pain, and 2) that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (39.4%). In addition, revising Question 11 (TIRF medicines should only be taken by patients who are opioid tolerant) to be specific to 'cancer' patients, resulted in a large decrease in correct response rate from the previous survey (85.2% to 43.5%) , which may indicate that some respondents were receiving TIRF medicine for non-cancer associated indications.

The consistently high level of patient understanding of key risk messages in the latest (48-month) survey indicates that the goals of the TIRF REMS are being met with existing tools. Due to the high level of understanding of these concepts by pharmacists and prescribers, no modifications to the educational program or Knowledge Assessment are recommended at this time (Section 8.2).

CONCLUSION

Based on the data provided in this TIRF REMS Access program assessment report (program and product utilization statistics, dispensing activity, program infrastructure and performance, non-compliance reporting, safety surveillance data and KAB surveys) the TRIG concludes that the REMS is meeting its established goals. Based on our analysis of the data for this 48-month assessment, the TRIG is recommending no REMS modifications at this time.

12 APPENDICES

12.1 Non-Compliance Protocol

TIRF REMS ACCESS PROGRAM NON-COMPLIANCE PROTOCOL

Version 7.0

October 26, 2015

Revision History

Version #	Date	Author	Description of Changes
1.0	February, 2012	(b) (6)	Initial Release

2.0	October 10, 2012	(b) (6)	• Added Revision History
			• Removed 'Draft-Review Required' Watermark
			• Added Sub-Sections to Section 5 (previously a separate document)
			  o Added 5.1 – Index of Scenarios
			  o Added 5.2 – Severity Reference
			  o Added 5.3 – Corrective Action Reference
			  o 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	(b) (6)	• 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	(b) (6)	• 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
			  o Revised the monitoring tool in Pharmacy Scenario 2 and Wholesaler/Distributor Scenario 1
			  o Revised Pharmacy Scenario 3

Version #	Date	Author	Description of Changes
			to be specific to suspended and deactivated stakeholders o Revised language in Pharmacy Scenarios 4, 5 & 6 for clarify o Added a new Pharmacy Scenario for altered claims o Revised Wholesaler/Distributor Scenario 1 to be specific to suspended and deactivated stakeholders o Revised language in Wholesaler/Distributor Scenario 2 for clarity o Revised Prescriber Scenario 1 to be specific to suspended and deactivated stakeholders o Revised language in Prescriber Scenario 2 for clarity o Re-defined 'timely manner' in Prescriber Scenario 2 o Revised language in Closed System Pharmacy Scenario 1for clarify o Added a Patient non-compliant scenario o Added an enrollment monitoring scenario for all stakeholders • Revised Section 5.4 – Reference – Monitoring Frequency Guidelines o Clarified new report requests will be handled via the Change Management Process o Changed 'Sponsor Data' to 'Sponsor Reporting' o Changed frequency of Sponsor Reporting from quarterly to every Non-Compliance Review Team Meeting and as needed o 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	(b) (6)	• Revised Section 5.1 – Non-Compliance Scenarios o Removed Pharmacy Scenario 4
4.0	5/24/13	(b) (6)	Accepted all changes from versions 3.1 and 3.2
4.1	8/7/13	(b) (6)	Added Section 6 – Non-Compliance Assessment Reporting
5.0	8/8/13	(b) (6)	• Accepted all changes from version 4.1 • Corrected page numbers
5.0	8/15/13	(b) (6)	• Approved by TRIG via vote during the 8/15/13 Program Status Call Meeting
5.1	12/17/13	(b) (6)	• Revised Section 5.1 – Non-Compliance Scenarios o Revised Prescriber Scenario 2 definition for 'complete PPAF on file in a timely manner' • Revised Section 5.3 – Reference – Corrective Action o Change 'annually' to 'within 12 months'
6.0	12/19/13	(b) (6)	• Accepted all changes from version 5.1
6.0	12/23/13	(b) (6)	• Approved via TRIG e-mail vote
6.1	12/5/13	(b) (6)	• Revised Section 5.1 – Non-Compliance Scenarios o Added Pharmacy Scenario 4: Pharmacy no longer has a valid DEA. o Added Prescriber Scenario 3: Prescriber no longer has a valid, schedule II DEA. o Added Prescriber Scenario 4: Prescribed TIRF medicines to an opioid non-tolerant individual. o 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 o Inclusion of language for repeat offenders when determined amount of time is reached without any suspected non-compliance activity o Grammatical corrections
7.0	10/26/15	(b) (6)	• Accepted all changes from version 6.1

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, will be 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 notice, 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 present 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 Teams and 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 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.

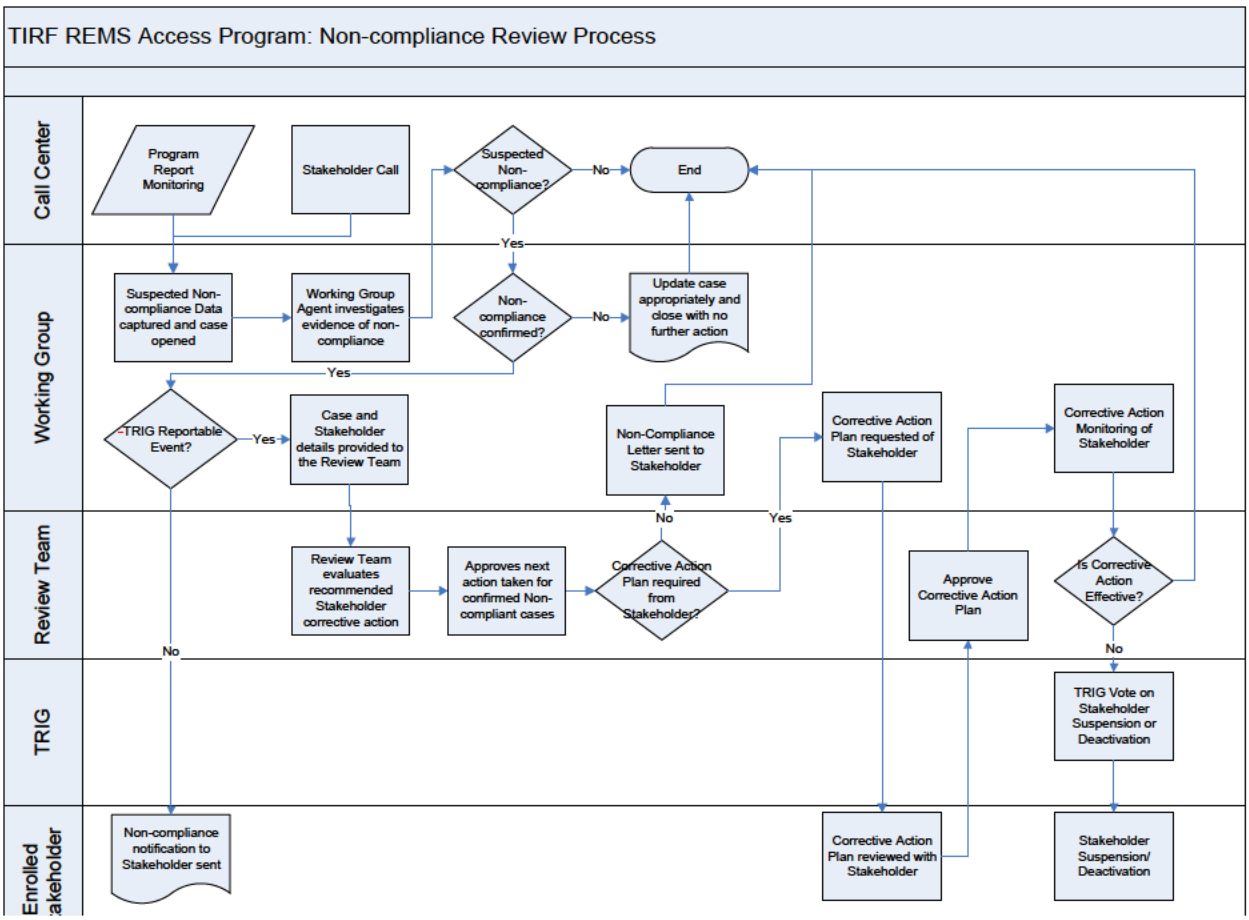
Stakeholders identified as having suspected or confirmed non-compliant events may be contacted by the Working Group via letters, phone calls or fax to resolve issues related to the identified program deviation all in accordance with such business rules.

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 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 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; notices, 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

An unintended (e.g., first-time) event. The corrective action will typically result in a written notice being sent to the stakeholder and re-education of the program requirements to prevent any re-occurrences of the event.

Moderate

A repeated event or a series of different [or distinct], unintended events. 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. Once implemented, the stakeholder will be monitored for compliance with the plan of action, and provided with a written warning for their files.

Serious

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. This level of offense will result in a suspension from the program and possible deactivation. 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. A deactivated stakeholder may request reinstatement in the TIRF REMS Access program.

Requests for reinstatement must be in writing and contain sufficient details of corrective actions taken to prevent any future incidents of non-compliance with elements of the program. Requests for reinstatement will be evaluated by the Review Team and the team will make the final determination on reinstatement.

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
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 (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from intial 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 reported
	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	First identification of a non-compliant event or since 24 months from the closure of a previous case.
Moderate	>1 non-compliance issue, without a warning on file
Serious	>1 non-compliance issue with a warning on file 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**
Notices	Patient notices will be sent to a patient's prescriber
	Minor violations that demonstrate a misunderstanding of the program requirements
	Notices are intended to re-educate stakeholders
	2 Notices in 60 days = Review by Non-Compliance Review Team to determine if a Warning is warranted
Warnings	Previous case resulted in a notice due to unsuccessful outreach attempts and unable to successfully outreach for current case.
	2 Warnings in 60 days = Review by Non-Compliance Review Team to determine if a Suspension is warranted
	>1 Warning and/or suspension in >60 days = Case-by-Case review for Suspension
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
	1 Warning or 2 Notices while Suspended = Review by Non-Compliance Review Team to determine if a Deactivation is warranted
	2 Suspensions within 12 months = Review by Non-Compliance Review Team to determine if a Deactivation is warranted
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

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.

12.2 Safety Surveillance Aggregate Line Listing Preferred Terms

I. Case Criteria:

- Only US cases
- No American Association of Poison Control Center (AAPCC) or literature search cases
- In addition to performing searches on the below preferred terms, sponsors will search for:
  - All cases with an outcome of death
  - Cases related to patients aged 0 through 18
- Cases to be included in the reporting period date range will be based on MedWatch Form field "Date Received by Manufacturer" (G4)

II. Case Identification

a. Addiction Line Listing

Cases of addiction will be identified through the following Preferred Terms. Sponsors are responsible for reviewing all cases pulled by these Preferred Terms and determining whether each is deemed as a case of addiction by their company. Only cases identified by a Sponsor's company as cases of addiction should be provided to UBC.

Preferred Terms for FDA Requested Cases of Addiction			
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**
Misuse			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Intentional drug misuse
Abuse			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug abuse
Inappropriate			
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered at inappropriate site

Preferred Terms for FDA Requested Cases of Addiction			
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Medication Error			
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dose administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dosage administered
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration
Accidental			
Injury, poisoning and procedural complications	Medication errors	Accidental exposures to product	Accidental exposure to product
Dependence			
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, antepartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, postpartum
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Polysubstance dependence

b. Overdose Line Listing

Cases of overdose will be identified through the following Preferred Terms.

Preferred Terms for FDA Requested Cases of Overdose			
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**
Overdose			
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Intentional overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Overdose
Injury, poisoning and procedural complications	Medication errors	Overdoses	Prescribed overdose
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Accidental poisoning

c. Death Line Listing

Cases of death will be identified through the following Preferred Terms or a reported outcome of death.

Preferred Terms for FDA Requested Cases of Death			
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**
Death			
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Accidental death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Brain death
General Disorders and administration site conditions	Fatal outcomes	Death and sudden death	Cardiac death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Death
General disorders and administrations site conditions	Fatal outcomes	Death and sudden death	Death neonatal
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden cardiac death
General Disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden death
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Agonal death struggle

Preferred Terms for FDA Requested Cases of Death			
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**
General disorders and administration site conditions	General system disorders NEC	General signs and symptoms NEC	Apparent death
General disorders and administration site conditions	Therapeutic and nontherapeutic effects (excl toxicity)	Therapeutic and nontherapeutic responses	Drug ineffective/death
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardio-respiratory arrest
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Breathing abnormalities	Respiratory arrest
Pregnancy, puerperium and perinatal conditions	Abortions and stillbirth	Stillbirth and foetal death	Foetal death

d. Pediatric Exposure Line Listing

Cases of pediatric exposure will be identified through the following Preferred Terms or any case involving patients 0-18 years of age.

Preferred Terms for FDA Requested Cases of Pediatric Exposure			
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**
Accidental			
Injury, poisoning and procedural complications	Medication errors	Accidental exposures to product	Accidental exposure to product by child
Injury, poisoning and procedural complications	Product use issues	Product use issues NEC	Drug administered to patient of inappropriate age
General disorders and administration site conditions	Product quality issues	Product packaging issue	Failure of child resistant mechanism for pharmaceutical product

e. Case Identification for Any Table Through Text-string Searches

In addition to the agreed upon Preferred Terms, Sponsors will also provide cases based on text-string searches using the below terms. Sponsors will inform UBC if cases are provided that are not aligned with the approved Preferred Terms, but were identified through a text-string search.

Text-string Search Terms for Narratives			
Addiction	Multiple drug overdose	Son	Nephew
Overdose	Expired	Daughter	Aunt
Drug dependence	Passed away	Grandmother	Uncle
Death	Infant	Grandfather	Mom
Pediatric exposure	Child	Sister	Pop
Died	Mother	Brother	Dad
Fatal	Father	Niece	Inappropriate Conversion
Inappropriate	Accidental	Intentional	Non-opioid Tolerant

12.3 Safety Surveillance Aggregate Line Listing of Deaths

Cases of Death Received from TRIG Sponsors during the Reporting Period: 29 August 2014 - 28 August 2015

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1472	19	Male	01JAN2012	29AUG2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1473	UNK	Male	Unknown	29AUG2014	Death	Cancer pain	Unknown	None reported	None reported	Death	Insufficient information
1475	UNK	Male	12AUG2014	01SEP2014	Death	Breakthrough pain	Unknown	None reported	None reported	Death	Not related
1477	UNK	Female	Unknown	02SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1480	61	Male	08SEP2014	10SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1482	66	Female	10SEP2014	16SEP2014	Death	Pain	Unknown	None reported	None reported	Death	Not related
1483	54	Male	29MAR2013	16SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1484	71	Male	12SEP2014	17SEP2014	Death	Breakthrough pain	2014-06 - UNK	None reported	None reported	Death	Insufficient information
1485	UNK	Female	Unknown	23SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1486	55	Unknown	Unknown	23SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1487	83	Female	Unknown	23SEP2014	Death, Hospice care	Severe pain related to malignancy	Unknown	None reported	None reported	Death	Not related
1488	49	Female	06JUN2014	23SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1489	57	Female	01MAY2014	23SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1490	UNK	Female	Unknown	24SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1491	UNK	Male	Unknown	25SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1492	64	Female	Unknown	25SEP2014	Ovarian cancer metastatic	Cancer pain	Unknown	None reported	None reported	Death	Not related
1493	51	Female	Unknown	26SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1494	50	Female	2014	26SEP2014	Disease progression	Breakthrough pain	Unknown	None reported	None reported	Death	Not related

48-month REMS Assessment Report
Transmucosal Immediate-Release Fentanyl (TIRF)
TIRF REMS Industry Group (TRIG) of Companies

Bold text indicates FDA requests/comments. Italicized text represents the response to each item.

1. **A more detailed data analysis section that presents the statistical methods used, how calculations were performed, and the assumptions made, at the level of detail as provided in your April 2, 2015, response to the March 19, 2015, FDA Information Request. In addition, include a pre-post REMS means analyses and trend analyses (e.g. segmented regression analyses), statistically comparing event rates for a time-period immediately prior to full implementation of the TIRF REMS with an equivalent period of time after REMS implementation.**

   As requested, a more detailed analysis section was added to the protocol. The detailed analysis section includes the additional requested means and trend analyses. FDA also requested that an equal number of quarter of data be included pre and post TIRF REMS. However this will not be possible for all programs. For example, there are now 12 quarters of data available post-REMS but as only 11 quarters of pre-TIRF REMS data are available for college survey. Please note that it is not a requirement of the model that an equal number of quarters are included pre and post TIRF REMS, but rather that there are enough quarters to model a trend in both the pre and post TIRF REMS period. To standardize and still represent an adequate period of time pre-TIRF REMS for trending we suggest including 8 quarters of data.

2. **Present the data at the dosage unit level as well as population and URDD levels.**

   We presented population, prescription, and dosing unit rates in the last report and will continue to provide these same rates for future reports. We did not include URDD rates as this scale is not necessarily additive. For example if a subject had both Actiq® and Fentora® prescribed in the same quarter, the de-identified aggregate data we receive from IMS would count this person twice instead of once thus failing to preserve uniqueness of subjects across drugs. Number of prescription and number of dosage units are additive.

3. **The RADARS treatment center data (Opioid Treatment Program and Survey of Key Informants Patients) programs are confounded by the fact that the number of treatment centers participating in each quarter fluctuates (although the overall numbers are generally increasing). In subsequent submissions, limit the presentation of treatment center data to centers that have contributed data in all of the time-periods assessed. In addition, provide the various versions of the survey instruments/pill cards in use throughout the time-periods assessed with dates provided indicating when each instrument was in use.**

   Based on analysis through 2Q15, limiting the data to only those treatment centers with respondents since 3Q09 will change the coverage region from roughly 349 treatment center sites to only 24 treatment center sites. Instead, we suggest presenting both the data for all centers, in addition to those 24 treatment centers, in order to judge the sensitivity of the result to the increasing number of treatment centers included in the two programs over time.

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1496	UNK	Male	Unknown	26SEP2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1498	61	Male	30MAY2014	29SEP2014	Neoplasm progression	Breakthrough pain	Unknown	None reported	None reported	Death	Not related
1501	UNK	Female	Unknown	03OCT2014	Death	Unknown	10 Years	None reported	None reported	Death	Not related
1502	52	Female	Unknown	03OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1503	72	Male	Unknown	03OCT2014	Metastasis, Bladder cancer	Unknown	Unknown	None reported	None reported	Death	Not related
1505	UNK	Male	Unknown	08OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1506	UNK	Male	Unknown	10OCT2014	Death	Unknown	2014-06 - UNK	None reported	None reported	Death	Insufficient information
1507	UNK	Female	Unknown	13OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1508	UNK	Male	Unknown	13OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1509	41	Female	07OCT2014	13OCT2014	Neoplasm progression	Breakthrough cancer pain	2014-10-02 - UNK	Advil, Ativan, Carafate, Dexamethasone, Emend, Lactulose, Marinol, Norco, Ondansetron, Oxycodone, Sancuso, Senokot, Temazepam, Warfarin, Fentanyl Patch	None reported	Death	Not related
1510	UNK	Female	Unknown	13OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1511	55	Male	01JUN2014	14OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1513	UNK	Male	2014	14OCT2014	Death	Breakthrough pain	2014-07-18 - UNK	None reported	None reported	Death	Not related
1514	UNK	Female	Unknown	14OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1515	UNK	Unknown	Unknown	15OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1517	59	Male	Unknown	16OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1518	60	Male	Unknown	17OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1520	68	Male	Unknown	22OCT2014	Death, Product use issue	Scoliosis, chronic pain	Unknown	None reported	None reported	Death	Not related
1521	UNK	Male	Unknown	23OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1522	69	Male	23OCT2014	23OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1523	UNK	Female	Unknown	23OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1524	79	Male	Unknown	23OCT2014	Prostate cancer	Cancer pain	Unknown	None reported	None reported	Death	Not related
1525	69	Male	24OCT2014	28OCT2014	Neoplasm progression	Cancer pain	Unknown	Morphine	None reported	Death	Not related
1526	UNK	Female	Unknown	29OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1527	66	Male	21OCT2014, Unknown	30OCT2014	Completed suicide, Off label use	Low back pain	Unknown	Methadone	None reported	Death	Insufficient information
1528	61	Female	22OCT2014	31OCT2014	Neoplasm progression	Lung cancer	2014-09 - UNK	Dexamethasone, Gilotrif, Percocet, Fentanyl Patch	None reported	Death	Not related
1529	69	Male	01JAN2014	03NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1530	78	Female	29MAR2014, 29MAR2014, 29MAR2014, 29MAR2014, 29MAR2014, 24MAR2014, 24MAR2014, Unknown	04NOV2014	Death, Gastrointestinal sounds abnormal, Lung infection, Traumatic lung injury, Urine output decreased, Atrial fibrillation, Respiratory failure, Somnolence	Unknown	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1531	52	Male	02MAY2013	05NOV2014	Neoplasm progression	Cancer pain	2012-12-27 - UNK	Afinitor, Albuterol, Amlodipine, Ativan, Celexa, Dilaudid, Exalgo ER, Phenergan, Relistor, Sennokot S	None reported	Death	Not related
1532	UNK	Male	Unknown	07NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1535	UNK	Male	Unknown	10NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1536	UNK	Female	Unknown	11NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1537	28	Male	Unknown	14NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1538	61	Female	01FEB2013	14NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1539	60	Male	Unknown	19NOV2014	Death	Pain	Unknown	None reported	None reported	Death	Not related
1541	64	Male	Unknown	20NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1542	UNK	Female	2013	20NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1543	UNK	Female	Unknown	20NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1546	UNK	Female	Unknown	21NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1548	71	Female	27APR2014	26NOV2014	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1549	UNK	Female	Unknown	26NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1550	UNK	Male	Unknown	26NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1551	UNK	Male	Unknown	01DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1552	UNK	Female	Unknown	08DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1554	52	Female	Unknown	15DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1555	UNK	Female	Unknown	18DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1556	UNK	Female	Unknown	19DEC2014	Disease progression	Cancer pain	Unknown	None reported	None reported	Death	Not related
1558	70	Female	23APR2013	23DEC2014	Neoplasm progression	Breakthrough cancer pain	2013-01-22 - UNK	Carboplatin, Complex B-100, Darbepoetin, Gemcitabine, Lisinopril, Ms-Contin, Oxycodone Hydrochloride, Paclitaxel, Potassium Chloride, Senna Plus, Vitamin D2	None reported	Death	Not related
1560	UNK	Male	Unknown	29DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1561	58	Female	Unknown	29DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1562	66	Female	31DEC2012	29DEC2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1563	72	Male	25DEC2014	05JAN2015	Neoplasm progression	Breakthrough cancer pain	2014-12-24 - UNK	Haldol, Morphine Concentrate, Oxycodone, Phenobarbital, Fentanyl Patch	None reported	Death	Not related
1564	UNK	Male	Unknown	07JAN2015	Death	Unknown	2014-03 - UNK	None reported	None reported	Death	Insufficient information
1565	UNK	Male	Unknown	08JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1566	67	Male	12JAN2015, 30NOV2014	12JAN2015	Death, Pneumonia	Pain	Unknown	Duragesic	None reported	Death	Not related
1567	65	Male	30NOV2014, 01FEB2013, Unknown	12JAN2015	Pneumonia, Lung cancer metastatic, Death	Pain	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1570	63	Male	Unknown	13JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1571	44	Female	Unknown	13JAN2015	Breast cancer metastatic	Cancer pain	Unknown	None reported	None reported	Death	Not related
1572	UNK	Female	Unknown	14JAN2015	Death	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Insufficient information
1573	UNK	Female	Unknown	14JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1574	46	Male	15JAN2015	15JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1575	84	Male	31MAR2014	16JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1576	UNK	Female	Unknown	20JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1577	56	Male	11JAN2015	20JAN2015	Death	Breakthrough cancer pain	Unknown	Fentanyl, Meropenem, Insulin	None reported	Death	Not related
1579	49	Female	Unknown	20JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1580	67	Male	JAN2013	22JAN2015	Cholecystitis, Septic shock, Death, Intentional product misuse, Hypotension, Ischaemic hepatitis, Rhabdomyolysis, Disseminated intravascular coagulation, Hepatic necrosis	Unknown	Unknown	None reported	APAP, Drug, Ethanol	Death	Not related
1581	83	Female	Unknown	23JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1582	UNK	Male	Unknown	27JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1583	UNK	Male	Unknown	27JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1584	UNK	Female	Unknown	27JAN2015	Uterine cancer	Unknown	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1585	UNK	Male	Unknown	29JAN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1587	50	Female	Unknown	30JAN2015	Breast cancer metastatic	Cancer pain, pain	Unknown	None reported	Morphine Sulfate, Fentanyl Transdermal System	Death	Not related
1588	47	Male	Unknown	02FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1589	UNK	Male	Unknown	02FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1590	74	Female	01JAN2013	05FEB2015	Death	Cancer pain	Unknown	None reported	None reported	Death	Not related
1591	33	Male	OCT2013	06FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1592	UNK	Female	DEC2014	09FEB2015	Death, Therapy cessation	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1593	UNK	Male	Unknown	11FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1595	UNK	Male	Unknown	16FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1596	32	Female	Unknown	17FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1597	UNK	Male	Unknown	18FEB2015	Neoplasm progression	Breakthrough cancer pain	Unknown	Oxycodone, Oxycontin	None reported	Death	Not related
1598	UNK	Male	Unknown	19FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1599	UNK	Female	Unknown	23FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1601	59	Male	Unknown	24FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1602	UNK	Male	Unknown	24FEB2015	Death	Unknown	2014-03 - UNK	None reported	None reported	Death	Insufficient information
1605	UNK	Female	Unknown	27FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1606	UNK	Male	Unknown	27FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1607	UNK	Male	Unknown	27FEB2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1610	32	Female	01AUG2007	12MAR2015	Accidental death	Pain	Unknown	Oxycontin, Dilaudid, Duragesic, Ambien, Klonopin, Seroquel	None reported	Death	Not related
1611	UNK	Female	Unknown	12MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1612	UNK	Male	Unknown	12MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1613	88	Female	Unknown	13MAR2015	Death	Cancer pain	Unknown	None reported	None reported	Death	Insufficient information
1615	UNK	Male	Unknown	17MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1616	UNK	Female	Unknown	17MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1617	51	Male	Unknown	17MAR2015	Malignant neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1618	60	Female	Unknown	18MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1620	51	Male	15MAY2013	19MAR2015	Death	Breakthrough cancer pain	29 Days	None reported	None reported	Death	Insufficient information
1621	UNK	Male	Unknown	19MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1622	UNK	Male	Unknown	19MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1623	UNK	Male	2013	20MAR2015	Colon cancer, Death	Breakthrough pain	Unknown	None reported	None reported	Death	Not related
1624	45	Female	01JAN2013	23MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1626	UNK	Female	Unknown	24MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1627	UNK	Female	Unknown	24MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1628	UNK	Female	Unknown	25MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1629	59	Female	Unknown	26MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1630	UNK	Female	Unknown	27MAR2015	Death	Breakthrough cancer pain	21 Days	None reported	None reported	Death	Not related
1631	UNK	Female	Unknown	27MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1632	UNK	Female	Unknown	31MAR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1633	UNK	Female	Unknown	01APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1634	UNK	Female	Unknown	01APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1635	UNK	Male	Unknown	01APR2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1636	UNK	Female	Unknown	02APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1637	45	Female	01JAN2013	03APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1638	76	Female	Unknown	06APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1639	UNK	Female	Unknown	07APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1640	47	Female	Unknown	08APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1641	60	Male	Unknown	09APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1645	51	Female	Unknown	21APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1646	UNK	Female	Unknown	22APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1647	58	Male	20NOV2013	24APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1648	41	Male	Unknown	27APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1649	32	Female	25APR2015	27APR2015	Neoplasm progression	Breakthrough cancer pain	2015-04-18 - UNK	Dilaudid, Fentanyl Patch	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1650	UNK	Unknown	Unknown	27APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1651	UNK	Male	Unknown	30APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1652	UNK	Male	Unknown	30APR2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1653	UNK	Female	Unknown	30APR2015	Neoplasm progression	Cancer pain	2013-06 - UNK	Arimidex, Herceptin	None reported	Death	Not related
1654	UNK	Female	Unknown	04MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1655	UNK	Female	Unknown	04MAY2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1656	UNK	Female	Unknown	06MAY2015	Death	Cancer	Unknown	None reported	None reported	Death	Not related
1657	UNK	Female	Unknown	06MAY2015	Malnutrition, Neoplasm progression	Breakthrough cancer pain	2014-09-26 - 2015-01-02	Amox-Tr-K Clv, Abraxane, Advair Diskus, Cyproheptadine, Digoxin, Dronabinol, Gemzar, Hydrocodone-Acetaminophen, Lisinopril, Lomotil, Marinol, Megace, Neulasta, Spiriva with Handihaler	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1658	UNK	Male	Unknown	06MAY2015	Malnutrition, Neoplasm progression	Breakthrough cancer pain	2014-07-16 - UNK	Allopurinol, Dexilant, Exforge, Gabapentin, Hydrocodone/Ibuprofen, Levothyroxine, Lidocaine, Lomotil, Magnesium, Megestrol, Metoclopramide, Metoprolol Succinate ER, Ondansetron, Potassium Chloride, Stivarga, Temazepam, Tramadol, Trilipix, Vitamin B-12, Duragesic	None reported	Death	Not related
1659	UNK	Female	Unknown	07MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1660	UNK	Male	Unknown	08MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1661	UNK	Female	Unknown	08MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1662	UNK	Male	Unknown	11MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1663	UNK	Unknown	Unknown	11MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1664	53	Male	Unknown	11MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1667	UNK	Male	Unknown	13MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1669	UNK	Female	Unknown	13MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1670	78	Male	15MAY2015	14MAY2015	Neoplasm progression	Pain	2015-04-23 - UNK	None reported	None reported	Death	Not related
1671	UNK	Male	Unknown	19MAY2015	Death	Colon cancer metastatic	Unknown	None reported	None reported	Death	Insufficient information
1672	47	Female	Unknown	19MAY2015	Breast cancer metastatic	Cancer pain	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1673	54	Female	Unknown	20MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1674	UNK	Male	Unknown	21MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1675	UNK	Male	Unknown	27MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1676	UNK	Female	Unknown	28MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1677	61	Female	Unknown	29MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1678	UNK	Female	Unknown	02JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1679	71	Female	Unknown	02JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1680	66	Male	Unknown	08JUN2015	Death	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related
1681	UNK	Male	Unknown	08JUN2015	Death	Unknown	2015-03-22 - UNK	None reported	None reported	Death	Insufficient information
1682	43	Male	Unknown	15JUN2015	Death	Breakthrough cancer pain	Unknown	Methadone, Oxycodone	None reported	Death	Insufficient information
1683	52	Female	Unknown	15JUN2015	Death	Breakthrough cancer pain	Unknown	Methadone, Oxycodone	None reported	Death	Insufficient information
1684	UNK	Female	Unknown	16JUN2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1686	67	Female	26JAN2015	16JUN2015	Neoplasm progression	Pain	Unknown	Caltrate 600/ Vitamin D, Carafate, Compazine, Diphenhydramine HCL, Docusate Calcium, Flaxseed Oil, Ibuprofen, Levothyroxine Sodium, Nexium, Oxycodone HCL, Pancrealipase, Potassium Gluconate, Prednisone, Pristiq, Promethazine HCL, Robaxin, Tamoxifen Citrate, Vitamin B-12, Vitamin D, Zofran, Fentanyl Patch	None reported	Death	Not related
1687	74	Male	24MAR2015	16JUN2015	Neoplasm progression	Cancer pain	2015-02-10 - UNK	Amlodipine Besylate, Calcitriol, Dexamethasone, Finasteride, Folic Acid, Marinol, Methadone HCL, Metoclopramide HCL, Miralax, Nexium, Ondansetron HCL, Oxycodone HCL, Senna Plus	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1688	85	Female	12APR2015	16JUN2015	Neoplasm progression	Pain, cancer pain	2015-03-20 - UNK	Amlodipine Besylate, Atenolol, Crestor, Dexamethasone, Folic Acid, Lasix, Methadone HCL, Mugard, Oxycodone HCL, Vitamin B-12, Xanax	None reported	Death	Not related
1689	UNK	Male	Unknown	16JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1690	69	Female	08AUG2013	18JUN2015	Death	Unknown	2015-03-22 - UNK	None reported	None reported	Death	Insufficient information
1691	82	Male	12JUN2015, Unknown, Unknown	18JUN2015	Death, Dementia, Malaise	Breakthrough cancer pain	2014-08-12 - UNK	None reported	None reported	Death	Not related
1692	UNK	Male	Unknown	19JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1693	UNK	Female	Unknown	22JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1694	85	Female	01NOV2013	29JUN2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related
1695	UNK	Female	Unknown	07JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1696	47	Male	25NOV2013	08JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1697	57	Male	16DEC2013	09JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1698	24	Female	2015	13JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1699	81	Male	04MAY2015, Unknown, Unknown	16JUL2015	Cardiac failure, Drug effect incomplete, Off label use	Thalamic pain	Unknown	Carvedilol, Fentanyl Patch	None reported	Death	Not related
1700	UNK	Male	Unknown	21JUL2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1701	UNK	Male	Unknown	21JUL2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1702	54	Male	14SEP2013	21JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1703	36	Male	15JUN2015	22JUL2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related
1705	51	Female	04AUG2013	23JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1706	UNK	Female	Unknown	24JUL2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1707	47	Female	06MAR2014	27JUL2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1708	UNK	Male	Unknown	27JUL2015	Terminal state	Pain	Unknown	None reported	None reported	Death	Not related
1709	UNK	Female	Unknown	27JUL2015	Death	Cancer pain	Unknown	Oxycontin	None reported	Death	Insufficient information
1710	64	Female	23DEC2013	28JUL2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related
1711	57	Male	06APR2014	29JUL2015	Neoplasm progression	Pain	2013-08-28 - UNK	None reported	None reported	Death	Not related
1712	UNK	Male	Unknown	04AUG2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1714	57	Female	Unknown	05AUG2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1715	48	Male	Unknown	10AUG2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1716	58	Male	Unknown	11AUG2015	Hepatic failure	Breakthrough pain	Unknown	None reported	None reported	Death	Insufficient information
1717	UNK	Female	Unknown	13AUG2015	Death	Unknown	2015-03-22 - UNK	None reported	None reported	Death	Insufficient information
1718	87	Male	11JAN2014	20AUG2015	Death	Breakthrough cancer pain	2013-09-11 - UNK	None reported	None reported	Death	Not related
1719	UNK	Male	Unknown	24AUG2015	Death	Unknown	Unknown	None reported	None reported	Death	Not related
1721	UNK	Male	MAY2015	24AUG2015	Death, Hospice care	Unknown	Unknown	None reported	None reported	Death	Insufficient information

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1722	UNK	Female	Unknown	25AUG2015	Neoplasm malignant, Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1724	50	Male	18SEP2013	27AUG2015	Metastatic neoplasm	Breakthrough pain	Unknown	None reported	None reported	Death	Insufficient information
1725	UNK	Female	Unknown	27AUG2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1729	UNK	Unknown	Unknown	29AUG2014	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1730	UNK	Male	Unknown	03SEP2014	Disease progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related
1731	56	Female	20AUG2014	10SEP2014	Disease progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related
1732	UNK	Male	Unknown	16SEP2014	Death	Metastatic bone pain	2014-08-20 - UNK	Cymbalta, Etravirine, Gabapentin, Lipitor, Ms-Contin, Periostat, Ritonavir, Trazodone, Truvada	None reported	Death	not related
1734	45	Female	04OCT2014	06OCT2014	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	not related
1735	63	Female	05OCT2014	06OCT2014	Neoplasm progression	Unknown	2014-09-17 - UNK	None reported	None reported	Death	Not related
1736	UNK	Male	Unknown	10OCT2014	Myocardial infarction, Neoplasm progression	Breakthrough cancer pain, pain	2014-10 - UNK	Declomycin, Dexamethasone, Diflucan, Doc-Q-Lace, Docusate, Fentanyl Patch	None reported	Death	not related
1737	UNK	Unknown	Unknown	27OCT2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1739	UNK	Unknown	Unknown	31OCT2014	Death	Breakthrough cancer pain	2014-10 - UNK	None reported	None reported	Death	Insufficient information
1740	UNK	Female	Unknown	04NOV2014	Neoplasm progression	Cancer pain	2014 - UNK	None reported	None reported	Death	not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1742	38	Male	05NOV2014, Unknown	10NOV2014	Death, Off label use	Pain	2013-11 - UNK	Morphine, Oxycodone	None reported	Death	Insufficient information
1743	UNK	Unknown	Unknown	20NOV2014	Neoplasm progression	Breakthrough cancer pain	2014-03-04 - UNK	None reported	None reported	Death	not related
1744	86	Female	28APR2014	25NOV2014	Death	Breakthrough cancer pain	2014-02-06 - UNK	None reported	None reported	Death	Insufficient information
1745	UNK	Female	Unknown	25NOV2014	Neoplasm progression	Cancer pain	2014-09-29 - UNK	None reported	None reported	Death	Not related
1747	48	Male	25NOV2014	25NOV2014	Neoplasm progression	Breakthrough cancer pain	2014-11-07 - UNK	None reported	None reported	Death	Not related
1748	UNK	Unknown	Unknown	26NOV2014	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient information
1749	57	Male	14NOV2014	26NOV2014	Neoplasm progression	Cancer pain	2014-11-03 - UNK	Oxycodone, Oxycodone/Acetaminophen, Valium	None reported	Death	Not related
1750	67	Female	28NOV2014	01DEC2014	Death	Breakthrough cancer pain	2014-09-29 - 2014-11-28	None reported	None reported	Death	Not related
1751	76	Female	18FEB2014, 23DEC2013	02DEC2014	Disease progression, Off label use	Chronic pancreatitis	2013-12-23 - 2014-01-23	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1752	UNK	Female	Unknown	05DEC2014	Death, Off label use	Chronic pain	2014-05-09 - UNK	Dilaudid, Furosemide, Glumetza, Imodium, Insulin, Kadian, Lyrica, Morphine Sulfate, Nitroglycerin, Orencia, Phenergan, Potassium, Pravastatin, Prednisone, Protonix, Singulair, Spironolactone, Synthroid, Vitamin B3, Xanax, Xarelto, Zebeta	None reported	Death	Not related
1753	UNK	Male	Unknown	13DEC2014	Neoplasm progression	Breakthrough cancer pain	Unknown	Dilaudid, Flonase, Marinol, Promethazine, Senokot-S, Viagra	None reported	Death	Not related
1754	UNK	Unknown	Unknown	17DEC2014	Neoplasm progression	Cancer pain	2014-11-13 - 2014-12-08	None reported	None reported	Death	Not related
1755	58	Female	22DEC2014	22DEC2014	Neoplasm progression	Cancer pain	Unknown	None reported	None reported	Death	Not related
1757	UNK	Unknown	Unknown	12JAN2015	Death	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Insufficient information
1758	UNK	Unknown	Unknown	12JAN2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related
1759	55	Male	13JAN2015, Unknown	13JAN2015	Death, Off label use	Chronic pain	Unknown	None reported	None reported	Death	Insufficient information
1760	UNK	Female	Unknown	16JAN2015	Neoplasm progression	Breakthrough cancer pain	2014-08-18 - UNK	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1762	47	Male	17JAN2015, Unknown	19JAN2015	Myocardial infarction, Off label use	Chronic pain	2014-11-19 - UNK	Clindamycin Hydrochloride, Cymbalta, Flexeril, Lyrica, Medrol, Norco, Oxycodone, Silvadene, Ultram, Duragesic	None reported	Death	Not related
1763	UNK	Unknown	Unknown	19JAN2015	Death, Off label use	Post laminectomy syndrome, coccydynia, fibromyalgia, chronic pain	2014-04-28 - UNK	None reported	None reported	Death	Insufficient information
1764	UNK	Unknown	Unknown	21JAN2015	Death	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related
1765	61	Female	18JAN2015, Unknown	23JAN2015	Chronic obstructive pulmonary disease, Off label use	Breakthrough pain, pain	2014-10-13 - UNK	Adavir Disku Aer, Ambien, Ativan, Azor, Brovana, Celebrex, Compazine, Cymbalta, Daliresp, Geodon, Hemocyte, Lamictal, Lopid, Oxycodone, Oxygen, Pravastatin, Prednisone, Provigil, Roxanol, Singulair, Sodium Chloride, Soma, Spiriva, Tylenol, Vitamin D, Xanax, Zofran, Duragesic	None reported	Death	Not related
1766	UNK	Male	Unknown	27JAN2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Not related
1767	UNK	Male	Unknown	02FEB2015	Neoplasm progression	Unknown	Unknown	None reported	None reported	Death	Not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1768	UNK	Female	Unknown	06FEB2015	Neoplasm progression	Cancer pain	2014-08-18 - UNK	None reported	None reported	Death	Not related
1769	UNK	Unknown	Unknown	10FEB2015	Neoplasm progression	Breakthrough cancer pain	2014-02-11 - UNK	None reported	None reported	Death	Not related
1770	73	Male	07FEB2015	24FEB2015	Myocardial infarction	Breakthrough cancer pain	Unknown	None reported	None reported	Death	Insufficient information
1771	49	Male	25FEB2015, 25FEB2015	26FEB2015	Death, Neoplasm progression	Breakthrough cancer pain	2015-02-05 - UNK	Lantus, Metformin, Omeprazole, Trilipix, Zestoretic	None reported	Death	Not related
1772	71	Male	28JAN2015	27FEB2015	Neoplasm progression	Cancer pain	2015-01-27 - UNK	None reported	None reported	Death	not related
1773	UNK	Female	Unknown	05MAR2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related
1775	UNK	Female	Unknown	23MAR2015	Neoplasm progression	Cancer pain	Unknown	None reported	None reported	Death	not related
1776	UNK	Female	Unknown	27MAR2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related
1777	67	Female	20MAR2015	27MAR2015	Neoplasm progression	Chronic pain	2015-02-24 - UNK	Calcium	None reported	Death	not related
1779	UNK	Unknown	Unknown	09APR2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1780	UNK	Male	Unknown	09APR2015	Neoplasm progression	Cancer pain	Unknown	None reported	None reported	Death	not related
1781	52	Female	02MAR2015	14APR2015	Death	Breakthrough cancer pain	2015-01-08 - UNK	None reported	None reported	Death	not related
1782	70	Female	15APR2015	16APR2015	Neoplasm progression	Cancer pain	Unknown	None reported	None reported	Death	not related
1783	UNK	Male	Unknown	20APR2015	Death, Off label use	Chronic pain	2015-04-01 - 2015-04-08	None reported	None reported	Death	not related
1784	UNK	Female	Unknown	20APR2015	Death, Off label use	Chronic pain	2015-02-25 - 2015-04-09	None reported	None reported	Death	not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1785	UNK	Female	Unknown	24APR2015	Off label use, Respiratory disorder, Sedation, Toxicity to various agents	Degenerative disc disease	Unknown	None reported	Exalgo	Death	Possibly related
1786	UNK	Female	Unknown	27APR2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related
1787	UNK	Male	Unknown	28APR2015	Neoplasm progression	Cancer pain	Unknown	None reported	None reported	Death	not related
1788	UNK	Male	Unknown	28APR2015	Hallucination, Neoplasm progression	Breakthrough cancer pain	2015-01 - UNK	None reported	None reported	Death	not related
1789	UNK	Male	Unknown	01MAY2015	Neoplasm progression	Breakthrough cancer pain	2014-08 - UNK	None reported	None reported	Death	not related
1790	UNK	Female	2015	01MAY2015	Neoplasm progression	Breakthrough cancer pain	2015-04-17 - UNK	None reported	None reported	Death	not related
1791	UNK	Male	Unknown	01MAY2015	Neoplasm progression	Breakthrough cancer pain	2015-04-17 - UNK	None reported	None reported	Death	not related
1792	UNK	Male	Unknown	01MAY2015	Neoplasm progression	Breakthrough cancer pain	2015-02-13 - UNK	None reported	None reported	Death	not related
1793	UNK	Female	Unknown	04MAY2015	Neoplasm progression	Breakthrough cancer pain	2015-04-28 - UNK	None reported	None reported	Death	not related
1794	UNK	Unknown	Unknown	06MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1795[2]	UNK	Female	Unknown	07MAY2015	Overdose	Unknown	Unknown	None reported	None reported	Death	Possibly related
1796	56	Female	07APR2015	11MAY2015	Neoplasm progression	Breakthrough cancer pain	2015-01-14 - UNK	Bupi, Clonidine, Dilaudid	None reported	Death	not related
1798	58	Female	08MAY2015	11MAY2015	Neoplasm progression	Unknown	2015-03-24 - 2015-05-06	None reported	None reported	Death	not related
1799	UNK	Female	Unknown	13MAY2015	Neoplasm progression	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1801	UNK	Unknown	Unknown	19MAY2015	Death, Off label use	Breakthrough pain	Unknown	None reported	None reported	Death	insufficient information
1803	UNK	Male	Unknown	21MAY2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1804	UNK	Male	Unknown	22MAY2015	Neoplasm progression	Breakthrough cancer pain	2015-03-09 - UNK	Amitiza, Aspirin, Calcium, Diazepam, Finasteride, Furosemide, Lyrica, Megace, Metoprolol, Potassium, Protonix, Sucralfate, Duragesic	None reported	Death	not related
1805	UNK	Unknown	Unknown	01JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1806	UNK	Unknown	Unknown	01JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1807	UNK	Female	Unknown	02JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1810	UNK	Male	Unknown	15JUN2015	Death	Unknown	Unknown	None reported	None reported	Death	insufficient information
1811	61	Male	26MAY2015	16JUN2015	Neoplasm progression	Colon cancer, carcinoma of liver, lung cancer	Unknown	None reported	None reported	Death	not related
1812	UNK	Male	Unknown	16JUN2015	Death	Breakthrough cancer pain	2015-05-11 - 2015-05-18	None reported	None reported	Death	not related
1813	56	Male	13JUN2015	18JUN2015	Death	Unknown	2015-05-27 - UNK	None reported	None reported	Death	not related
1816	63	Female	16JUN2015, Unknown	25JUN2015	Neoplasm progression, Pneumonia	Breakthrough cancer pain	2015-03-25 - 2015-06-08	None reported	None reported	Death	not related

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[1]
1817	65	Female	28MAY2015	29JUN2015	Neoplasm progression	Breakthrough cancer pain	2015-05-04 - UNK	Atenolol, Ativan, Diovan, Levothyroxine, Lexapro, Omeprazole, Zofran	None reported	Death	not related
1818	62	Male	29JUN2015, 29JUN2015, Unknown, Unknown	01JUL2015	Cardiac arrest, Myocardial infarction, Chest pain, Haemoptysis	Breakthrough cancer pain	Unknown	Cimex, Klonopin, Losartan Hctz, Mobic, Omeprazole, Spiriva Inhaler, Tessalon, Ventolin Inhaler, Fentanyl Patch	None reported	Death	not related
1820	68	Male	14JUL2015	14JUL2015	Neoplasm progression	Breakthrough cancer pain	2015-07-07 - UNK	None reported	None reported	Death	not related
1821	68	Female	11JUL2015	28JUL2015	Neoplasm progression	Breakthrough cancer pain	2015-06-08 - UNK	None reported	None reported	Death	not related
1822	UNK	Female	Unknown	03AUG2015	Death	Cancer pain	2015-04-27 - UNK	None reported	None reported	Death	not related
1824	UNK	Male	Unknown	10AUG2015	Neoplasm progression	Breakthrough cancer pain	2015-05 - UNK	None reported	None reported	Death	not related
1826	53	Female	22AUG2015	25AUG2015	Neoplasm progression	Breakthrough cancer pain	2014-12 - 2015-08	None reported	None reported	Death	not related
1828	UNK	Female	25AUG2015	28AUG2015	Neoplasm progression	Unknown	2015-07-02 - UNK	None reported	None reported	Death	not related
1829	UNK	Male	Unknown	24JUL2015	Cardiac disorder	Breakthrough cancer pain	Unknown	Horizant, Oxycontin	None reported	Death	not related
1830	UNK	Male	Unknown	27JUL2015	Hepatic failure	Breakthrough cancer pain	Unknown	None reported	None reported	Death	not related

[1] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
[2] Patient 1795 is also described in the table for overdose (Table 29 of the Assessment Report).
Unk = unknown.

12.4 RMPDC Responses to FDA Requests

48-month REMS Assessment Report
Transmucosal Immediate-Release Fentanyl (TIRF)
TIRF REMS Industry Group (TRIG) of Companies

Bold text indicates FDA requests/comments. Italicized text represents the response to each item.

1. **A more detailed data analysis section that presents the statistical methods used, how calculations were performed, and the assumptions made, at the level of detail as provided in your April 2, 2015, response to the March 19, 2015, FDA Information Request. In addition, include a pre-post REMS means analyses and trend analyses (e.g. segmented regression analyses), statistically comparing event rates for a time-period immediately prior to full implementation of the TIRF REMS with an equivalent period of time after REMS implementation.**

   As requested, a more detailed analysis section was added to the protocol. The detailed analysis section includes the additional requested means and trend analyses. FDA also requested that an equal number of quarter of data be included pre and post TIRF REMS. However this will not be possible for all programs. For example, there are now 12 quarters of data available post-REMS but as only 11 quarters of pre-TIRF REMS data are available for college survey. Please note that it is not a requirement of the model that an equal number of quarters are included pre and post TIRF REMS, but rather that there are enough quarters to model a trend in both the pre and post TIRF REMS period. To standardize and still represent an adequate period of time pre-TIRF REMS for trending we suggest including 8 quarters of data.

2. **Present the data at the dosage unit level as well as population and URDD levels.**

   We presented population, prescription, and dosing unit rates in the last report and will continue to provide these same rates for future reports. We did not include URDD rates as this scale is not necessarily additive. For example if a subject had both Actiq® and Fentora® prescribed in the same quarter, the de-identified aggregate data we receive from IMS would count this person twice instead of once thus failing to preserve uniqueness of subjects across drugs. Number of prescription and number of dosage units are additive.

3. **The RADARS treatment center data (Opioid Treatment Program and Survey of Key Informants Patients) programs are confounded by the fact that the number of treatment centers participating in each quarter fluctuates (although the overall numbers are generally increasing). In subsequent submissions, limit the presentation of treatment center data to centers that have contributed data in all of the time-periods assessed. In addition, provide the various versions of the survey instruments/pill cards in use throughout the time-periods assessed with dates provided indicating when each instrument was in use.**

   Based on analysis through 2Q15, limiting the data to only those treatment centers with respondents since 3Q09 will change the coverage region from roughly 349 treatment center sites to only 24 treatment center sites. Instead, we suggest presenting both the data for all centers, in addition to those 24 treatment centers, in order to judge the sensitivity of the result to the increasing number of treatment centers included in the two programs over time.

12.5 RADARS System Program Report Protocol

RADARS® SYSTEM

Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS): Surveillance Monitoring Protocol

For

Actavis Laboratories FL, Inc.
BioDelivery Sciences International, Inc.
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
Depomed, Inc.
Galena Biopharma, Inc.
Insys Therapeutics Inc.
Mallinckrodt Pharmaceuticals
Mylan, Inc.
Par Pharmaceutical, Inc.

October 1, 2015

Confidential

DENVER HEALTH
Level One Care for ALL

RMPDC
ROCKY MOUNTAIN POISON & DRUG CENTER
Saving Lives with Answers

7. Appendices

7.1 Shell Tables

Table x.x.x

The RADARS® System xxx Program

xxxx Pre Post Comparison Means Model

From July 2010 to Current

Drug group	Pre-TIRM REMS Mean (10Q3 to 12Q2)	Post-TIRF REMS Mean (12Q3 to current)	Rate Ratio(95% CI)	p-value for % change	p-value for interaction
Population Adjusted Rate per 100,000 population					
TIRF Products	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II IR Opioids	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II Opioids	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II Opioids Excluding Methadone	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Prescription Adjusted Rate per 10,000 prescriptions					
TIRF Products	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II IR Opioids	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II Opioids	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II Opioids Excluding Methadone	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Dose Unit Adjusted Rate per 100,000					
TIRF Products	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II IR Opioids	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II Opioids	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx
Schedule II Opioids Excluding Methadone	xxx (xxx-xxx)	xxx (xxx-xxx)	xxx (xxx-xxx)	xxxx	xxxx

Table x.x.x
The RADARS® System xxx Program
xxx Trend Model
From July 2010 to Current

	Intercept					Slope				
Drug Group	**Pre**	**Post**	**% change (95% CI)**	**p-value for difference**	**p-value for interaction**	**Pre**	**Post**	**% change (95% CI)**	**p-value for difference**	**p-value for interaction**
Population										
TIRF Products	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II IR Opioids	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II Opioids	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II Opioids Excluding Methadone	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Prescription Adjusted Rate										
TIRF Products	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II IR Opioids	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II Opioids	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II Opioids Excluding Methadone	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Dose Unit Adjusted Rate										
TIRF Products	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II IR Opioids	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II Opioids	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx
Schedule II Opioids Excluding Methadone	x.xxx	x.xxx	xx.xx%(xx.xx%,xx.xx%)					xx.xx%(xx.xx%,xx.xx%)	x.xxx	x.xxx

Table x.x.x
Cumulative Mention Rates per 100,000 Population, 10,000 Prescriptions and 100,000 Dose Units
2012Q3-XXXXQX

	Total	
Cumulative Rates	**Pre TIRF REMS July 2010-June 2012**	**Post TIRF REMS July 2012-current**
Poison Center Abuse Cases/Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
Treatment Center Surveys Cases/Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
Opioid Treatment Program Cases/Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
Survey of Key Informant Cases/Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
College Survey Cases/Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
Impaired Healthcare Worker Program Cases	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxx	x.xxx

Table x.x.x
The RADARS System Poison Center Program
Reported Deaths by Age Group and Period
2012Q3-XXXXQX

Age Group	Pre TIRF REMS July 2010-June 2012	Post TIRF REMS July 2012- current
0-5 years	3 (3)	1 (1)
6-12 years	0 (0)	0 (0)
13-19 years	1 (1)	3 (3)

Mentions (Cases)

Table x.x.x
The RADARS System Poison Center Program
Reported Deaths by Age, Medical Outcome and Period
2012Q3-XXXXQ2

Time Period	Case Number	Year Quarter	Age Group	Exposure Reason	Medical Outcome
2010Q3-2013Q3	72917219	20123	<=5 years	Unintentional General	No effect
	72969297	20123	<=5 years	Unintentional General	Minor effect
	73034925	20124	<=5 years	Unintentional General	Minor effect
	1975719	20123	13-19 years	Intentional Abuse	Moderate effect
2013Q4-2014Q2	8239739	20142	<=5 years	Unintentional Therapeutic Error	Not followed, minimal clinical effects possible
	58064	20141	13-19 years	Intentional Misuse	Major effect
	1219402	20142	13-19 years	Intentional Abuse	Moderate effect
	1787732	20142	13-19 years	Intentional Abuse	Not followed, minimal clinical effects possible

Time Period	Case Number	Year Quarter	Age Group	Exposure Reason	Medical Outcome
XXXXQX-XXXXQX					
XXXXQX-XXXXQX					

12.6 RADARS System Program Report

RADARS® SYSTEM REPORT

Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS): Surveillance Monitoring

December 6, 2015

DENVER HEALTH
Level One Care for ALL

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ROCKY MOUNTAIN POISON & DRUG CENTER
Saving Lives with Answers

FOLLOWING THIS PAGE, FDA_2814 TO FDA_3187 WITHHELD IN FULL AS B(4)/CCI

12.7 Periodic Stakeholder Surveys

12.7.1 Patient KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Patient Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number:	Wave 4, 48-month REMS Assessment Version 1.0
Survey Time Period:	24 July 2015 to 03 September 2015
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. (BDSI) Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	15 December 2015

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
BDSI	BioDelivery Sciences International
CI	Confidence Interval
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Professional
KAB	Knowledge, Attitudes and Behavior
N/A	Not Applicable
PPAF	Patient-Prescriber Agreement Form
PBM	Pharmacy Benefits Manager
REMS	Risk Evaluation and Mitigation Strategy
SCC	Survey Coordinating Center
SD	Standard Deviation
TIRF	Transmucosal Immediate Release Fentanyl
TIRF Medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

Executive Summary

The 48-month Knowledge, Attitudes, and Behavior (KAB) survey for patients receiving Transmucosal Immediate Release Fentanyl (TIRF) medicines or their caregivers was conducted as part of the 48-Month TIRF Risk Evaluation and Mitigation Strategy (REMS) Access Program Assessment. The survey launched on 24 July 2015 and closed on 03 September 2015. Food and Drug Administration (FDA) feedback was provided in the 36-month Assessment Report Acknowledgement Letter and where applicable these changes were implemented in the 48-month survey. Changes included removing 'Onsolis' as a response option throughout the survey because it is no longer available, moving specified existing survey questions under key risk messages, and including an analysis of demographics of the patient survey respondents compared to the demographics of patients receiving a TIRF product.

The specific goals of the TIRF medicines patient/caregiver KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients/caregivers regarding TIRF medicines. The focus of the survey included the following: 1) TIRF medicines can cause life-threatening breathing problems that can lead to death, patients should take TIRF medicines only if they are opioid-tolerant, and patients should strictly follow the directions of the Healthcare Professional (HCP), 2) patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to an HCP, 3) patients should not give TIRF medicines to anyone else even if they have the same symptoms, and 4) TIRF medicines should be stored in a safe place away from children and properly disposed. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the Patient-Prescriber Agreement Form (PPAF).

Invitations (and reminders) were sent to all known patients/caregivers who had filled a prescription within the 4 months (120 days) prior to survey launch. From the total of 432 patients/caregivers who accessed the survey, 314 (72.7%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (98.7%) completed the survey, exceeding the target of 300 completed surveys. The geographic distribution of survey respondents was similar to the general population of TIRF users (comparison requested by FDA).

In general, there is an overall trend across all patient/caregiver KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward maintenance or improvement in patient/caregiver knowledge and understanding of the key risk messages. Of the 19 components included as part of key risk messages, 13 components had a response rate >80%, and 3 components had a correct response rate between 67.7% and 74.8% . The remaining 3 components within key risk messages 2 and 3 had a correct response rate which fell below the desired threshold of 65%. Patients scored consistently low on two of 19 components across all survey waves which included 1) *TIRF medicines should not be taken for long-lasting pain not from cancer, like arthritis joint pain* and 2) *a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.* In addition, revising one question (TIRF medicines should only be taken by patients who are opioid tolerant) to be specific to '*cancer'* patients, resulted in a large decrease in the correct response rate, which may indicate that some respondents were receiving TIRF medicine for a non-cancer associated indications.

The consistently high level of patient understanding of key risk messages in this 48-month survey indicates that the goals of the TIRF REMS Access Program are being met with existing tools. The TIRF REMS Industry Group (TRIG) will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

1. PATIENT SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics indicated for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The FDA has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program was approved by the FDA on 28 December 2011. This report describes the results from the patient surveys conducted for the 48-Month TIRF REMS Access Program Assessment, and reflects the reporting period of 29 October 2014 to 28 October 2015. The 48-month KAB survey launched on 24 July 2015 and closed on 03 September 2015.

The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and their generic equivalents. The TRIG includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. Two companies joined the TRIG during the reporting period: Actavis Laboratories FL, Inc. joined on 6 February 2015 and BDSI replaced Meda Pharmaceuticals on 11 March 2015.

The TIRF REMS Access Program consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. 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 the following:

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.

An important component of the TIRF REMS Access Program Assessment is the conduct of quantitative evaluation surveys to assess patients'/caregivers' understanding and knowledge of the safe use of TIRF medicines as described in the TIRF REMS Access Program educational materials. Administration of the surveys conducted among patients/caregivers enrolled in the TIRF REMS Access Program is described in the protocol (See Appendix A). Note: Protocol and Survey question revisions from the 36-month assessment report are identified as tracked changes.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

1.1 Changes to the KAB Survey for Patients/Caregivers Based on FDA Feedback

FDA Feedback was received on the KAB survey for patients/caregivers in the 36-month Assessment Report Acknowledgement Letter received by the TRIG sponsors on 04 August 2015. FDA requested the following be implemented in the 48-month survey and analysis:

- Remove Onsolis as a response option throughout the survey as it is no longer available
- Move an existing survey question (Question 10a-e) into Key Risk Message 3
- Move Question 13b from Key Risk Message 2 to Key Risk Message 3
- Include an analysis of demographics of the patient survey respondents compared to the demographics of patients receiving a TIRF product

The patient/caregiver KAB Survey invitations were distributed upon survey launch on 24 July 2015. Although the FDA feedback was received on 04 August 2015 after the launch of the survey, the removal of "Onsolis" as a response option was successfully completed during the survey data collection period with no impact to patients/caregivers taking the survey or the survey results presented in this report. In addition to this survey change, the FDA requests related to the allocation of questions to key risk messages for analysis were successfully implemented and are included in this report.

The remaining FDA request was to provide an analysis of how the demographics of the patient survey respondents compare to the demographics of actual TIRF patients. Due to timing of the request and the time required to obtain these data, this information was unable to be included in the 48-Month FDA Assessment Report. As communicated to FDA on 09 September 2015, the TRIG plans to submit a Supplemental Report to FDA to include items that were unable to be included in this assessment report based on the timing of the 36-Month FDA Assessment Report Acknowledgement Letter. A comparison of geographic data between survey respondents and the general population of TIRF patients are included in this report; the full demographic comparison will be included in the Supplemental Report estimated to be delivered on May 4, 2016.

2. PATIENT SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients regarding the following key information and risk messages communicated through the REMS:

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 not 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.

This survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and PPAF.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions developed to test patient understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, provided in Appendix A.

3.1 Survey Sample

A sample of 300 patients treated with TIRF medicines was planned for this fourth KAB survey which was expected to be open from 24 July 2015 to 20 October 2015. This lengthened survey period (in comparison to previous years) was planned in an effort to meet the survey goal, which had not been achieved in some previous waves. The survey sample size was determined based on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

This survey was conducted on patients identified from the TIRF REMS Access Program database and a Pharmacy Benefits Manager (PBM). All patients 18 years or older who filled one or more prescriptions for at least one of the TIRF medicines during the 120 days prior to 24 July 2015 were eligible to participate; caregivers (age 18 years or older) of eligible patients who were unable to take the survey for themselves were eligible to participate. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation

(UBC), or the FDA were not eligible to participate; nor were any respondents who participated in the previous waves of the survey (the 12-month TIRF REMS Access Program Assessment, the 24-month TIRF REMS Access Program Assessment, or the 36-month TIRF REMS Access Program Assessment).

3.1.2 Recruitment

Patients who were passively enrolled in the TIRF REMS Access Program as of 30 June 2015 and had received a TIRF medicine in the previous 4 months (120 days) were invited to participate via an invitation letter sent through the United States Postal Service (USPS) (see Section 5.1.1 for more details). Address verification was required on these data due to the limited data points collected through the PPAF. In order to obtain this additional information a public records database was used and those data combined with the TIRF REMS Access Program data were used to distribute invitations to the patient population. Additional patients were identified for participation through a PBM partner, which provided a broad demographic coverage and included patients in 49 states. Through use of these sources, a list was created of patients who had filled a prescription for a TIRF medicine within 4 months (120 days) prior to survey launch (first prescriptions and refills). Full details are provided in the protocol (Appendix A).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; thus additional mailings were distributed to non-respondents from the original sample to maximize participation.

Each letter of invitation included a unique code needed to access the survey. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed).

Patients were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. The survey was estimated to take approximately 20 minutes to complete.

All respondents who completed the survey and provided their contact information were mailed a $50 gift card for participating. The mailing included a thank you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the patients'/caregivers' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I don't know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, only patient questions are presented in the key risk messages tables below. The same questions, with modified wording as appropriate for caregivers, are presented in the survey protocol (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's/caregiver's knowledge that TIRF medicines can cause life-threatening breathing problems.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the patient's/caregiver's awareness that TIRF medicines should be taken only by opioid-tolerant adult patients.

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired response**
	Please answer True, False, or I don't know for the following statement:	
11	TIRF medicines should only be taken by patients who are opioid tolerant.	***True***
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	***True***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's/caregiver's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired response**
10	For which of the following conditions should you use a TIRF medicine?	
10a	Headache or migraine pain	***No***
10b	Breakthrough pain from cancer	***Yes***
10c	Dental pain	***No***
10d	Pain after surgery	***No***
10e	Long-lasting pain not from cancer, like arthritis joint pain	***No***
12	Please answer True, False, or I don't know for each of the following statements.	
12b	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	***True***
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	***False***
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	***True***
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	***False***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's/caregiver's knowledge of the interchangeability of TIRF medicines.

Key Risk Message 4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	***False***

3.2.5 Key Risk Message 5

Key Risk Message 5 refers to the patient's/caregiver's awareness that TIRF medicines should not be given to anyone else even if they have the same symptoms.

Key Risk Message 5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	***False***
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	***True***

3.2.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's/caregiver's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed.

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	***True***
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	***True***
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	***True***
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	***Get emergency help right away.***

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible patients/caregivers who completed the survey. Eligible respondents were defined as those respondents who answered Yes to Question 1 (agree to take part in survey), Yes to Question 2 (filled a prescription for a TIRF medicine in the last 4 months) or Yes to Question 3 (caregiver for someone who had filled a prescription for a TIRF medicine in the last 4 months), and No to Question 5 (participated in past survey), and No to Question 8 (worked for a TRIG company, UBC, or FDA). Respondents also must have selected an age group ≥18 years of age for Question 6 (patient and caregiver). A survey was considered "completed" when an eligible patient/caregiver answered all relevant questions.

4.2 Primary Analyses

Primary analyses were performed for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/component included in the key risk message. Confidence intervals (95% CI) were calculated using the exact binomial method around the percentage of correct responses.

Primary analyses were then stratified by questions/characteristics of interest:

1) Those who indicated they both received the Medication Guide and read most of it versus those who responded No or I don't know or who received it and read only some of it or answered I don't know (Questions 18, 23, and 24).
2) Those who indicated they understood all or most of the Medication Guide versus those who understood some of it versus those understood none or did not know if they understood versus those who did not know whether they received or read the Medication Guide (Question 25).
3) Whether the survey was completed via the internet or telephone.
4) Highest level of education (Question 37).
5) Age group of respondent (Question 6).

Stratified analyses were conducted only when at least two of the stratified response categories had at least 50 respondents (e.g., for analysis 3 above, at least 50 respondents had to respond they completed the survey via the internet and at least 50 had to respond they completed it by telephone in order for that analysis to be conducted).

4.3 Secondary Analyses

As an indicator of the overall level of comprehension of the entire key risk message, descriptive analyses of the number and percentage of responders who answered various proportions of the key risk message components correctly are presented (e.g., the proportion who answered one question in the key risk message correctly, those who answered two questions correctly, those who answered three component questions correctly, etc.). Confidence intervals (95% CI) were calculated for the proportion of respondents who answered all component questions of the key risk message correctly.

4.4 Patient Report of a Potential Adverse Event, Product Complaint, or Medical Information Request during the Survey

A patient or caregiver may have reported a potential adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the adverse event or complaint, the verbatim response, and the respondent's contact information, if provided. The respondent was also informed that a representative from the appropriate TIRF medicine sponsor may contact him/her to obtain additional information about the event. Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted

an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Unless otherwise indicated, data tables contain the question presented to the patients. Analyses were summarized by overall population, and not by type of respondent (patient vs. caregiver) since only 4 caregivers participated in the survey.

Results of the patient's/caregiver's responses to questions in the KAB survey are summarized in this section; stratified analysis tables and overall listings are provided in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

Survey recruitment was performed using the names obtained through the TIRF REMS Access Program database and a PBM (See Section 3.1 for survey methodology details). Based on the number of prescriptions filled or refilled during the 120 days prior to survey implementation (24 July 2015), the TIRF REMS Access Program database identified 4993 potential participants and the PBM identified 576 potential participants. As shown in Table 1, all 5569 possible participants were sent a survey invitation letter. A total of 447 reminder letters were sent to non-responders (some potential participants may have received more than one reminder letter). Successful survey recruitment through leveraging data collected by the TIRF REMS Access Program (as described in Section 3.1), resulted in the patient/caregiver KAB survey closing early on 03 September 2015 once 310 surveys were collected.

From the total of 432 patients/caregivers who accessed the survey, 314 (72.7%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (98.7%) completed the survey. Of the 310 respondents who completed the survey, 194 (62.6%) completed the survey online, and 116 (37.4%) completed it by telephone (Table 3).

Table 1. Survey Participant Administration Results

Summary Statistic	N	%
Number of invitations distributed	5569	
Number of invitations returned as undeliverable	148	
Number of reminder letters distributed	447	
All Respondents [1]	432	8.0
Eligible Respondents [2]	314	72.7
Completed survey [3]	310	98.7

Table 1. Survey Participant Administration Results

Summary Statistic	N	%
Did not complete the survey [3]	4	1.3
Respondents not eligible [2, 4]	118	27.3

[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.

[2] Percentage is based on the number of all respondents.

[3] Percentages are based on the number of eligible respondents.

[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

As shown in Table 2, of the 432 respondents who accessed the survey, 374 patients/caregivers answered at least 1 survey question, and 58 respondents did not answer any of the survey questions and were discontinued. Of the 432 prescribers who started the survey, 373 agreed to participate. During the screening process it was determined 60 of the 374 respondents who answered at least 1 survey question were not eligible to participate in the survey because they either did not agree to participate in the survey (1 respondent), indicated that they had not or did not know whether they filled a prescription for a TIRF medicine within the last 4 months either for themselves or as a the caregiver of a patient (16 respondents), that they had participated in or did not know whether they participated in a survey about TIRF medicines before (41 respondents), or that they or an immediate family member had worked for a TRIG company, the FDA, or UBC (1 respondent). In addition, 1 of the 432 respondents who answered at least 1 survey question discontinued the survey at Question 2. Thus, there were 314 eligible participants (patients/caregivers) (Table 2); 310 respondents (98.7%) completed the survey (Table 1).

Table 2. Survey Participant Screening Results

Question	Patients/Caregivers (N=432)	
	n	%
Question 1: Do you agree to take part in this survey?		
Yes	373	86.3
No [1]	1	0.2
Discontinued	58	13.4

Table 2. Survey Participant Screening Results

Question	Patients/Caregivers (N=432)	
	n	%
Question 2: Within the last 4 months (120 days), have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of any of these brands.		
Yes	352	81.5
No	14	3.2
I don't know	6	1.4
Question not asked [2]	1	0.2
Discontinued	59	13.7
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months (120 days)? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands.		
Yes	4	0.9
No [1]	15	3.5
I don't know [1]	1	0.2
N/A (Answered "Yes" to Question 2)	352	81.5
Question not asked [2]	1	0.2
Discontinued	59	13.7
Question 5: Have you ever taken part in a survey about a TIRF medicine before?		
Yes [1]	29	6.7
No	315	72.9
I don't know [1]	12	2.8
Question not asked [2]	17	3.9
Discontinued	59	13.7
Question 6: Which of the following groups best describes your age?		
Under 18 [1]	0	
18 - 29	5	1.2
30 - 39	20	4.6

Table 2. Survey Participant Screening Results

Question	Patients/Caregivers (N=432)	
	n	%
40 - 49	66	15.3
50 - 59	132	30.6
60 - 69	76	17.6
70 or older	16	3.7
Prefer not to answer [1]	0	
Question not asked [2]	58	13.4
Discontinued	59	13.7
Question 7: Which of the following groups best describes the patient's age? [3]		
Under 16	0	
16 - 29	0	
30 - 39	0	
40 - 49	1	0.2
50 - 59	0	
60 - 69	2	0.5
70 or older	1	0.2
Prefer not to answer [1]	0	
Question not asked [2]	369	85.4
Discontinued	59	13.7
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply. [4]		
Actavis Laboratories FL, Inc. [1]	0	
Anesta LLC [1]	0	
BioDelivery Services International (BDSI) [1]	0	
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd.) [1]	1	0.2
Depomed, Inc. [1]	0	
Galena Biopharma, Inc. [1]	0	

Table 2. Survey Participant Screening Results

Question	Patients/Caregivers (N=432)	
	n	%
Insys Therapeutics, Inc. [1]	0	
Mallinckrodt Pharmaceuticals [1]	0	
McKesson Specialty Care Solutions [1]	0	
Mylan, Inc. [1]	0	
Par Pharmaceutical, Inc. [1]	0	
RelayHealth [1]	0	
Teva Pharmaceuticals, Ltd. [1]	0	
United BioSource Corporation [1]	0	
FDA (Food and Drug Administration) [1]	0	
No [5]	314	72.7
I don't know [1]	0	
Question not asked [2]	58	13.4
Discontinued	59	13.7

[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question or skip pattern.
[3] Only caregivers are asked this question.
[4] More than one response can be selected, so percentages may not sum to 100%.
[5] Ineligible if selected in addition to another response.
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

Those taking the survey online took a mean of 14 minutes to complete it, while those taking it by telephone took a mean of 21 minutes (Table 3).

Table 3. Time to Complete Survey for Completers Only

Time to Complete Survey for Completers (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total [1]**
N	116	194	310
Mean (± SD)	21.69 (9.062)	14.42 (8.677)	17.14 (9.487)
Minimum	14.1	4.5	4.5
Median	19.61	12.81	16.47
Maximum	102.3	85.8	102.3
Category			
0 – <5 Minutes	0	2	2
5 – <10 Minutes	0	52	52
10 – <15 Minutes	1	81	82
15 – <20 Minutes	68	30	98
20 – <25 Minutes	31	12	43
25 – <30 Minutes	7	9	16
30 Minutes or More	9	8	17

[1] Number of eligible respondents completing the survey (Table 1).

5.1.2 Patient/Caregiver Demographics

The demographic characteristics of respondents who completed the survey are shown in Table 4. The largest number of patients (128; 41.3%) were 50 – 59 years of age. More than half of the respondents (176; 56.8%) were females, and 247 (79.7%) respondents had at least some college or an Associate's degree or higher education. Prescriptions for Subsys® (146; 33.8%) and Actiq® including generic versions (127; 29.4%) were filled most frequently in the 4 months preceding the survey. Most participants (117; 37.7%) were from the South, followed by the West (81; 26.1%), Midwest (61; 19.7%) and Northeast (51; 16.5%), regions of the United States (US) (Table 4).

Based on FDA feedback, the patient survey was updated to remove Onsolis® as a response option throughout the survey as it is no longer available. Prior to this removal, 2 patients selected Onsolis® as a response for Question 4. These responses were removed from the analysis, and the change was not considered to have affected the overall survey results (See Section 1.1).

Table 4. Description and Representativeness of Eligible Patients/Caregivers

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months (120 days)? Please select all that apply.		
Abstral	15	3.5
Actiq, including generic versions of Actiq	127	29.4
Fentora	66	15.3
Lazanda	19	4.4
Subsys	146	33.8
Other	15	3.5
I don't know	1	0.2
Question not asked [2]	17	3.9
Discontinued	59	13.7
Respondent's age based on Question 6: Which of the following groups best describes your age?		
18 - 29	5	1.6
30 - 39	19	6.1
40 - 49	65	21.0
50 - 59	129	41.6
60 - 69	76	24.5
70 or older	16	5.2
Patient's age based on Question 6/7: Which of the following groups best describes your age/the patient's age?		
Under 16	0	
16 - 29	5	1.6
30 - 39	19	6.1
40 - 49	65	21.0
50 - 59	128	41.3
60 - 69	77	24.8

Table 4. Description and Representativeness of Eligible Patients/Caregivers

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
70 or older	16	5.2
Question 36: What is your gender?		
Male	133	42.9
Female	176	56.8
Prefer not to answer	1	0.3
Question 37: What is the highest level of education you have completed?		
Less than high school	4	1.3
Some high school	7	2.3
High school graduate/GED	48	15.5
Some college/Associates' degree	123	39.7
Bachelor's degree	71	22.9
Master's degree	38	12.3
Professional or Doctoral degree	15	4.8
Prefer not to answer	4	1.3
Question 38: What is the main language you speak at home?		
English	309	99.7
French	0	
Spanish	0	
Portuguese	0	
Italian	0	
German	0	
Chinese	0	
Japanese	0	

Table 4. Description and Representativeness of Eligible Patients/Caregivers

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Korean	0	
Other	0	
Prefer not to answer	1	0.3
Question 39: Are you Hispanic or Latino?		
Yes	9	2.9
No	296	95.5
Prefer not to answer	5	1.6
Question 40: For informational purposes only, which of the following U.S. census categories best describes your race?		
American Indian or Alaska Native	3	1.0
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	2	0.6
Black or African American	15	4.8
Native Hawaiian or Other Pacific Islander	3	1.0
White	265	85.5
Other	4	1.3
Prefer not to answer	11	3.5
Two or more races	7	2.3
Geographic Distribution (based on Question 41 - In which state do you live?) [3]		
Northeast	51	16.5
Midwest	61	19.7
South	117	37.7

Table 4. Description and Representativeness of Eligible Patients/Caregivers

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
West	81	26.1
Other	0	
Prefer not to answer	0	

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Question not asked due to termination response from a previous question or skip pattern.

[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

5.1.2.1 Comparison of Survey Respondents to the General Population of TIRF Users

Comparison of the survey respondents to the general population of TIRF users (as requested by the FDA) showed the geographic distribution of respondents to the patient survey was similar to the overall population of TIRF users (Table 5).

Table 5. Comparison of Survey Respondents to General Population of TIRF Users

Question	Eligible/Completed Patients & Caregivers (N=310) n (%)	Patients Who Have Taken a TIRF Medicine in the Last 4 Months (120 days) [1] (N=9858) n (%)
Geographic Distribution [2]		
Northeast	51 (16.5)	1811 (18.4)
Midwest	61 (19.7)	1305 (13.2)
South	117 (37.7)	4021 (40.8)
West	81 (26.1)	2706 (27.4)
Other	0	0

Table 5. Comparison of Survey Respondents to General Population of TIRF Users

Question	Eligible/Completed Patients & Caregivers (N=310) n (%)	Patients Who Have Taken a TIRF Medicine in the Last 4 Months (120 days) [1] (N=9858) n (%)
Prefer not to answer	0	0
Missing	0	15 (0.2)

[1] Based on data obtained from the TIRF REMS Access Program database.

[2] Based on Patient KAB Survey Question 41; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Note: Percentages are based on the patients and caregivers with informative data.

5.1.3 TIRF Medicines Education Materials

Respondents were asked about their awareness of educational materials about TIRF medicines, specifically the Medication Guide (Table 6), and the Patient-Prescriber Agreement Form (Table 7). Of the 310 respondents, 298 (96.1%) reported they had received the Medication Guide for the TIRF medicine prescribed for them. Of these 298 respondents, 174 respondents (58.4%) reported receiving the Medication Guide from their doctor or doctor's office, with 146 respondents (83.9%) receiving it at the first appointment with the prescribing doctor. Most respondents (250; 83.9%) reported receiving the Medication Guide from their pharmacy with 230 of these respondents (92.0%) stating they received the Medication Guide each time a prescription was filled.

Of the 298 respondents who received the Medication Guide, most respondents (287; 96.3%) indicated they read the Medication Guide; of these 287 respondents 273 respondents (95.1%) read all of it or most of it, and 263 respondents (91.6%) indicated understanding all or most of the Medication Guide. Over half of the respondents who received the Medication Guide (171; 57.4%) indicated someone offered to explain the medication guide to them; of these, 123 respondents (71.9%) indicated the doctor or someone in the doctor's office offered to explain the Medication Guide and 127 respondents (74.3%) indicated their pharmacist offered to explain the Medication Guide. Of the 171 respondents, 119 (69.6%) indicated they accepted the offer to have the Medication Guide explained to them, and of those 119 respondents, 117 (98.3%) indicated they understood all or most of the explanation. A total of 16 (5.4%) respondents

indicated they had questions about the information in the Medication Guide (See Appendix B, Listing 3).

Table 6. Responses to Questions About TIRF Medication Guide

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Question 18: Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?		
Yes	298	96.1
No	7	2.3
I don't know	5	1.6
Question 19: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office? [2]		
Yes	174	58.4
No	106	35.6
I don't know	18	(6.0)
N/A (Answered "No" or "I don't know" to Question 18)	12	
Question 20: When was the Medication Guide given to you? Please select all that apply. [2,3]		
At the first appointment with the doctor who prescribed the TIRF medicine	146	83.9
At the last appointment with the doctor who prescribed the TIRF medicine	23	13.2
I don't remember	24	13.8
N/A (answered "No" or "I don't know" to Question 18 or 19)	136	
Question 21: Did you receive the Medication Guide for the TIRF medicine from the pharmacy? [2]		
Yes	250	83.9
No	33	11.1
I don't know	15	5.0
N/A (Answered "No" or "I don't know" to Question 18)	12	
Question 22: How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy? [2]		
Only with the first filled prescription	8	3.2
Each time a prescription is filled	230	92.0

Table 6. Responses to Questions About TIRF Medication Guide

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Other (please specify):[4]	3	1.2
I don't know	9	3.6
N/A (Answered "No" or "I don't know" to Question 18 or 21)	60	
Question 23: Did you read the Medication Guide? [2]		
Yes	287	96.3
No	8	2.7
I don't know	3	1.0
N/A (Answered "No" or "I don't know" to Question 18)	12	
Question 24: How much did you read? [2]		
All of it	198	69.0
Most of it	75	26.1
Some of it	13	4.5
I don't know	1	0.3
N/A (Answered "No" or "I don't know" to Question 18 or 23)	23	
Question 25: How much of the Medication Guide did you understand? [2]		
All of it	155	54.0
Most of it	108	37.6
Some of it	23	8.0
None of it	0	
I don't know	1	0.3
N/A (Answered "No" or "I don't know" to Question 18 or 23)	23	
Question 26: Did someone offer to explain the Medication Guide to you? [2]		
Yes	171	57.4
No	111	37.2
I don't know	16	5.4
N/A (Answered "No" or "I don't know" to Question 18)	12	

Table 6. Responses to Questions About TIRF Medication Guide

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Question 27: Who offered to explain the Medication Guide to you? Please select all that apply. [2]		
The doctor or another healthcare professional in the doctor's office	123	71.9
The pharmacist where the TIRF medicine prescription was filled	127	74.3
Someone else [5]	15	8.8
N/A (Answered "No" or "I don't know" to Question 18 or 26)	139	
Question 28: Did you accept the offer to have the Medication Guide explained to you? [2]		
Yes	119	69.6
No	49	28.7
I don't know	3	1.8
N/A (Answered "No" or "I don't know" to Question 18 or 26)	139	
Question 29: How much of the explanation did you understand? [2]		
All of it	92	77.3
Most of it	25	21.0
Some of it	2	1.7
None of it	0	
I don't know	0	
N/A (Answered "No" or "I don't know" to Question 18, 26 or 28)	191	
Question 30: Did you or do you have any questions about the information in the Medication Guide? [2]		
Yes [6]	16	5.4
No	277	93.0

Table 6. Responses to Questions About TIRF Medication Guide

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
I don't know	5	1.7
N/A (Answered "No" or "I don't know" to Question 18)	12	

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Verbatim text for 'other' for how frequently the Medication Guide is received from the pharmacy (Question 22) is presented in Appendix B, Listing 1.
[5] Verbatim text for other persons offering to explain the Medication Guide (Question 27) is presented in Appendix B, Listing 2.
[6] Questions about the information in the Medication Guide (Question 30) are presented in Appendix B, Listing 3.

The responses to Questions 22, 27 and 30 are listed in Appendix B, Listing 1, Appendix B, Listing 2, and Appendix B, Listing 3, respectively.

5.1.4 Patient-Prescriber Agreement Form

After respondents were asked questions regarding the key risk messages, they were asked if they had received, read, and understood the PPAF. A total of 256 respondents (82.6%) indicated that someone at the doctor's office had explained the PPAF to them, and of the 256 respondents, 204 respondents (79.7%) understood all of it and 44 (17.2%) understood most of it. The PPAF was signed by 248 respondents (80.0%); of the 248 respondents, 180 responders (72.6%) reported receiving a copy of the signed PPAF (Table 7).

Table 7. Responses to Questions About the Patient-Prescriber Agreement Form

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Question 32: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?		
Yes	256	82.6
No	27	8.7
I don't know	27	8.7

Table 7. Responses to Questions About the Patient-Prescriber Agreement Form

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Question 33: How much of the explanation did you understand? [2]		
All of it	204	79.7
Most of it	44	17.2
Some of it	4	1.6
None of it	1	0.4
I don't know	3	1.2
N/A (Answered "No" or "I don't know" to Question 32)	54	
Question 34: Did you sign a Patient-Prescriber Agreement Form?		
Yes	248	80.0
No	13	4.2
I don't know	49	15.8
Question 35: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form? [2]		
Yes	180	72.6
No	27	10.9
I don't know	41	16.5
N/A (Answered "No" or "I don't know" to Question 34)	62	

[1] Number of eligible respondents completing the survey (See Table 1).
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

5.2 Key Risk Messages

5.2.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's/caregiver's knowledge that TIRF medicines can cause life-threatening breathing problems that can lead to death.

Most patients/caregivers (91.9%, (95% CI: 88.3- 94.7) were aware of the risk of life-threatening breathing problems with TIRF medicines (Table 8).

Analyses stratified by whether the Medication Guide was received and read (Received and read: N=273; Did not receive or read: N=37), and if the Medication Guide was read and understood (Understood most or all N=263, Understood some N=23, Did not understand N=1, Did not receive or read N=23) were not performed for any of the key risk messages because they did not meet the criteria of ≥50 respondents within at least two response categories.

No trends were evident when the results for Key Risk Message 1 were stratified by modality for completing the survey (internet versus telephone), respondent highest level of education, and by the age group of the respondent (Appendix B).

Table 8. Key Risk Message 1: TIRF Medicines Can Cause Life-Threatening Breathing Problems That Can Lead to Death

Question	Eligible/Completed Patients & Caregivers N=310 [1]	
	n	% (95% CI) [2]
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 / the patient.		
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
True [3]	285	91.9 (88.3 - 94.7)
False	3	1.0
I don't know	22	7.1

[1] Number of eligible respondents completing the survey (See Table 1).
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3].Indicates the correct response(s) to each question or component within a question.

5.2.2 Key Risk Message 2

Key Risk Message 2 refers to the patient's/caregiver's knowledge that the patient should not take TIRF Medicines if they are not opioid tolerant. Two components defined this key risk message (Table 9).

Less than half of the respondents understood that TIRF medicines should only be taken by *cancer* patients who are opioid tolerant (43.5%, 95% CI: 38.0-49.3). This question was reworded from the previous survey to specify the patients as '*cancer*' patients.

Most respondents (90.3%, 95% CI: 86.5-93.4) correctly indicated that opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.

Overall, 41.6% (95% CI: 36.1-47.3) provided correct responses for both components of Key Risk Message 2.

Table 9. Key Risk Message 2: Patients Should Not Take TIRF Medicines if They Are Not Opioid Tolerant

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
Question 11: Please answer True, False, or I don't know for the following statement:		
TIRF medicines should only be taken by cancer patients who are opioid tolerant.		
True [3]	135	43.5 (38.0 - 49.3)
False	122	39.4
I don't know	53	17.1
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.		
True [3]	280	90.3 (86.5 - 93.4)
False	14	4.5
I don't know	16	5.2
Secondary Analyses: Number of Correct Responses		
0 correct responses	24	7.7
1 correct response	157	50.6
2 correct responses	129	41.6 (36.1 - 47.3)

[1] Number of eligible respondents completing the survey (See Table 1).

[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method..

[3] Indicates the correct response(s) to each question or component within a question.

There was a trend toward a higher correct response rate for Question 11 in respondents that took the survey via the internet (Table 10) and a trend toward a higher correct response rate for Question 11 and Component 12a in respondents with a higher education (Table 11). No trends were evident when the results for Key Risk Message 2 were stratified by by the age group of the respondent (Appendix B).

Table 10. Trends in Correct Response Rates by Modality for Completing the Survey (Internet versus Telephone)

Question	Stratification Question			
	Modality			
	Internet (N=194)		Telephone (N=116)	
	Correct Response Rate		Correct Response Rate	
	n	% ([95% CI) [1]	n	% (95% CI) [1]
Key Risk Message 2				
11. TIRF medicines should only be taken by cancer patients who are opioid tolerant.				
True	94	48.5 (41.2 - 55.7)	41	35.3 (26.7 - 44.8)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 11. Trends in Correct Response Rates by Highest Level of Education

Question	Stratification Question							
	Highest Level of Education							
	GED or less (N=63)		College (N=123)		BA/BS or MS/MA (N=109)		Professional or Doctoral Degree (N=15)	
	Correct Response Rate		Correct Response Rate		Correct Response Rate		Correct Response Rate	
	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% ([95% CI) [1]
Key Risk Message 2								
11. TIRF medicines should only be taken by cancer patients who are opioid tolerant.								
True	25	39.7 (27.6-52.8)	51	41.5 (32.7-50.7)	52	47.7 (38.1 - 57.5)	7	46.7 (21.3 - 73.4)
12a. Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.								
True	51	81.0 (69.1-89.8)	112	91.1 (84.6-95.5)	104	95.4 (89.6 - 98.5)	13	86.7 (59.5 - 98.3)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

5.2.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's/caregiver's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider. Nine components define this key risk message (Table 12).

For Components 10a-10e, which in previous surveys were not included as part of a key risk message, most respondents understood that TIRF medicines should not be used for headache or migraine pain (80.6%, 95% CI: 75.8-84.9) or dental pain (90.3%, 95% CI: 86.5-93.4). Over half of the respondents understood the TIRF medicines should not be used for pain after surgery (67.7%, 95% CI: 62.2-72.9). Less than half (43.9%, 95% CI: 38.3-49.6) of respondents indicated they were aware that TIRF medicines are not indicated for long-lasting painful conditions not caused by cancer; however, 68.4% (95% CI: 62.9-73.5) knew that TIRF medicines should be used for breakthrough pain from cancer.

In response to Component 12b, 122 respondents (39.4%, 95% CI: 33.9-45.0) understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.

For Component 13b, 74.8% of respondents (95% CI: 69.6-79.6) correctly indicated that it is not okay for patients to take TIRF medicines for headache pain, and all respondents (100%, 95% CI: 98.8-100.0) understood that TIRF medicines should be taken exactly as prescribed by the doctor.

For Component 17b, 86.1% (95% CI: 81.8 - 89.8) knew that is not okay to take TIRF medicines for short-term pain that will go away in a few days.

Overall, 15.8% (95% CI: 11.9-20.4) correctly answered all components of the key risk message; 33.9% missed no more than one component, and 52.2% missed no more than two of the nine components.

Table 12. Key Risk Message 3: TIRF Medicines Should be Taken Exactly as Prescribed by the Healthcare Provider

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
Question 10: For which of the following conditions should you use a TIRF medicine?		
10a: Headache or migraine pain		
Yes	32	10.3
No [3]	250	80.6 (75.8 - 84.9)
I don't know	28	9.0
10b: Breakthrough pain from cancer		
Yes [3]	212	68.4 (62.9 - 73.5)
No	80	25.8
I don't know	18	5.8
10c: Dental pain		
Yes	8	2.6
No [3]	280	90.3 (86.5 - 93.4)
I don't know	22	7.1
10d: Pain after surgery		
Yes	65	21.0

Table 12. Key Risk Message 3: TIRF Medicines Should be Taken Exactly as Prescribed by the Healthcare Provider

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
No [3]	210	67.7 (62.2 - 72.9)
I don't know	35	11.3
10e: Long-lasting pain not from cancer, like arthritis joint pain		
Yes	135	43.5
No [3]	136	43.9 (38.3 - 49.6)
I don't know	39	12.6
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True [3]	122	39.4 (33.9 - 45.0)
False	93	30.0
I don't know	95	30.6
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.		
13b: It is OK for patients to take TIRF medicines for headache pain.		
True	20	6.5
False [3]	232	74.8 (69.6 - 79.6)
I don't know	58	18.7
13c: TIRF medicines should be taken exactly as prescribed by the doctor.		
True [3]	310	100.0 (98.8-100.0)
False	0	
I don't know	0	

Table 12. Key Risk Message 3: TIRF Medicines Should be Taken Exactly as Prescribed by the Healthcare Provider

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.		
True	13	4.2
False [3]	267	86.1 (81.8 - 89.8)
I don't know	30	9.7
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	3	1.0
2 correct responses	9	2.9
3 correct responses	12	3.9
4 correct responses	15	4.8
5 correct responses	40	12.9
6 correct responses	69	22.3
7 correct responses	57	18.4
8 correct responses	56	18.1
9 correct responses	49	15.8 (11.9-20.4)

[1] Number of eligible respondents completing the survey (See Table 1).
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Indicates the correct response(s) to each question or component within a question.

There was a trend toward a higher correct response rate for Components 12b and 13b in respondents with a higher education (Table 13). No trends were evident when the results for Key Risk Message 3 were stratified by modality for completing the survey (internet versus telephone) and by the age group of the respondent (Appendix B).

Table 13. Trends in Correct Response Rates by Highest Level of Education

Question	Stratification Question							
	Highest Level of Education							
	GED or less (N=63)		College (N=123)		BA/BS or MS/MA (N=109)		Professional or Doctoral Degree (N=15)	
	Correct Response Rate		Correct Response Rate		Correct Response Rate		Correct Response Rate	
	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% ([95% CI) [1]
Key Risk Message 3								
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.								
True	12	19.0 (10.2-30.9)	48	39.0 (30.4-48.2)	54	49.5 (39.8 - 59.3)	8	53.3 (26.6 - 78.7)
13b: It is OK for patients to take TIRF medicines for headache pain.								
False	43	68.3 (55.3-79.4)	88	71.5 (62.7-79.3)	92	84.4 (76.2-90.6)	9	60.0 (32.3-83.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

5.2.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's/caregiver's knowledge that they must not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider (Table 14).

Of the 310 respondents, 95.2% (95% CI: 92.1-97.3) understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

Table 14. Risk Message 4: Patients Should Not Switch From a TIRF Medicine to Another Medicine That Contains Fentanyl Without Talking to a Healthcare Provider

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.		
True	5	1.6
False [3]	295	95.2 (92.1 - 97.3)
I don't know	10	3.2

[1] Number of eligible respondents completing the survey (See Table 1).
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Indicates the correct response(s) to each question or component within a question.

There was a trend toward a higher correct response rate for Component 12c in respondents with higher education (Table 15). No trends were evident when the results for Key Risk Message 4 were stratified by modality for completing the survey (internet versus telephone) and by the age group of the respondent (Appendix B).

Table 15. Trends in Correct Response Rates by Highest Level of Education

Question	Stratification Question							
	Highest Level of Education							
	GED or less (N=63)		College (N=123)		BA/BS or MS/MA (N=109)		Professional or Doctoral Degree (N=15)	
	Correct Response Rate		Correct Response Rate		Correct Response Rate		Correct Response Rate	
	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% ([95% CI) [1]
Key Risk Message 4								
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.								
False	54	85.7 (74.6-93.3)	119	96.7 (91.9-99.1)	107	98.2 (93.5 - 99.8)	15	100.0 (78.2 - 100.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

5.2.5 Key Risk Message 5

Key Risk Message 5 refers to patient's/caregiver's knowledge that TIRF medicines should not be given to anyone else even if they have the same symptoms (Table 16).

For Component 12d, 99.4% (95% CI: 97.7 - 99.9) understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient, and 98.7% (95% CI: 96.7 - 99.6) understood that selling or giving away TIRF medicines is against the law (Component 17a).

Overall, 98.1% (95% CI: 95.8-99.3) correctly answered both components of the key risk message.

No trends were evident when the results for Key Risk Message 5 were stratified by modality for completing the survey (internet versus telephone), respondent highest level of education, and by the age group of the respondent (Appendix B).

Table 16. Key Risk Message 5: Patients Should Not Give TIRF Medicines to Anyone Else Even if They Have the Same Symptoms

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.		
True	0	
False[2]	308	99.4 (97.7 - 99.9)
I don't know	2	0.6
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17a: Selling or giving away TIRF medicines is against the law.		
True[2]	306	98.7 (96.7 - 99.6)
False	2	0.6
I don't know	2	0.6
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	6	1.9
2 correct responses	304	98.1 (95.8-99.3)

[1] Number of eligible respondents completing the survey (See Table 1).
[2] All confidence intervals are exact binomial 95% confidence intervals.
[3] Indicates the correct response(s) to each question or component within a question.

5.2.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's/caregiver's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed (Table 17).

Almost all respondents (99.7%, 95% CI: 98.2-100.0) correctly responded that TIRF medicines should be stored in a safe place out of the reach of children (Component 13a). Most respondents

(88.1%, 95% CI: 83.9-91.5) correctly indicated they should get emergency help right away if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine (Question 14), and 96.5% (95% CI: 93.7 - 98.2) understood that TIRF medicines must be disposed of as described in the specific product's Medication Guide (Component 17c). In addition, 93.2% (95% CI: 89.8 - 95.8) understood that a TIRF medicine can cause an overdose and death in any child who takes it (Component 17e).

Overall, 81.3% correctly answered all components of the key risk message.

Table 17. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
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.		
13a: TIRF medicines should be stored in a safe place out of the reach of children.		
True [3]	309	99.7 (98.2-100.0)
False	1	0.3
I don't know	0	
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)		
Wait an hour and see if the person is OK.	6	1.9
Get emergency help right away. [3]	273	88.1 (83.9 - 91.5)
Do nothing.	1	0.3
I don't know.	30	9.7
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.		
True [3]	299	96.5 (93.7 - 98.2)
False	2	0.6

Table 17. Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	% (95% CI) [2]
I don't know	9	2.9
17e: A TIRF medicine can cause an overdose and death in any child who takes it.		
True [3]	289	93.2 (89.8 - 95.8)
False	2	0.6
I don't know	19	6.1
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	2	0.6
2 correct responses	8	2.6
3 correct responses	48	15.5
4 correct responses	252	81.3 (76.5-85.5)

[1] Number of eligible respondents completing the survey (See Table 1).
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Indicates the correct response(s) to each question or component within a question.

There was a trend toward a higher correct response rate for Question 14 in respondents with a higher education (Table 18). No trends were evident when the results for Key Risk Message 4 were stratified by modality for completing the survey (internet versus telephone) and by the age group of the respondent (Appendix B).

Table 18. Trends in Correct Response Rates by Highest Level of Education

Question	Stratification Question: Highest Level of Education							
	GED or less (N=63)		College (N=123)		BA/BS or MS/MA (N=109)		Professional or Doctoral Degree (N=15)	
	Correct Response Rate		Correct Response Rate		Correct Response Rate		Correct Response Rate	
	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% ([95% CI) [1]
Key Risk Message 6								
14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)								
Get emergency help right away	52	82.5 (70.9-90.9)	109	88.6 (81.6-93.6)	98	89.9 (82.7 - 94.9)	14	93.3 (68.1 - 99.8)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

5.2.7 Other Survey Questions

5.2.7.1 Additional Questions about TIRF Medicines Safety

Table 19 summarizes the patient/caregiver responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. The results generally indicate that respondents were educated by a HCP on the precautions to be taken to ensure safe use of TIRF medicines. See Section 5.2 for all key risk message question results.

The majority of respondents (83.5%) indicated someone in the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine.

Most respondents (95.5%) indicated that someone in the doctor's office explained how to use the prescribed TIRF medicines and 82.3% indicated someone in the doctor's office advised them on the proper storage of the prescribed TIRF medicines. The majority (76.1%) were also aware that TIRF medicines are only available through the TIRF REMS Access Program.

Table 19. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible/Completed Patients & Caregivers (N=310) [1]	
	n	%
Question 9: Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands.		
Yes	259	83.5
No	36	11.6
I don't know	15	4.8
Question 15: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?		
Yes	296	95.5
No	9	2.9
I don't know	5	1.6
Question 16: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?		
Yes	255	82.3
No	49	15.8
I don't know	6	1.9
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17d: TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access Program).		
True	236	76.1
False	8	2.6
I don't know	66	21.3

[1] Number of eligible respondents completing the survey (See Table 1).

[2] Indicates the correct response(s) to each question or component within a question.

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N=310; Table 1), there were 34 reports of a potential adverse event or product complaint associated with the use of TIRF medicines made during a telephone interview or while activating a gift card via telephone (29 reports), or within the survey free text field during the online survey (5 reports). Verbatim statements are provided in Appendix B, Listing 4.

6. DISCUSSION AND CONCLUSIONS

Discussion

Survey invitations (and reminders) were sent to all known patients/caregivers who had filled a prescription within the 4 months prior to survey launch. From among the 310 who responded to the invitation, 306 patients and 4 caregivers completed the survey.

The specific goals of the TIRF medicines patient/caregiver KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients/caregivers regarding TIRF medicines. The focus of the survey included the following: 1) TIRF medicines can cause life-threatening breathing problems that can lead to death, patients should take TIRF medicines only if they are opioid-tolerant, and patients should strictly follow the directions of the HCP, 2) patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to an HCP, 3) patients should not give TIRF medicines to anyone else even if they have the same symptoms, and 4) TIRF medicines should be stored in a safe place away from children and properly disposed. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the PPAF.

Comparison of the survey respondents to the general population of TIRF users (as requested by FDA) showed the geographic distribution of respondents to the patient survey was similar to the overall population of TIRF users (Table 5). A full comparison of demographics of the survey respondents to the general population of TIRF users will be included in the Supplemental Report estimated to be delivered on May 4, 2016.

Of the 19 components included as part of key risk messages, 13 components had a response rate >80%, and 3 components had a correct response rate between 67.7% and 74.8%. The remaining 3 components within key risk messages 2 and 3 had a correct response rate which fell below the desired threshold of 65%.

Question 11 in the 36-month survey was worded: '*TIRF medicines should only be taken by patients who are opioid tolerant*' and scored 85.2%. Prior to this survey implementation, it was reworded to '*TIRF medicines should only be taken by cancer patients who are opioid tolerant*' and scored 43.5%. Since a high percentage of respondents understood the definition of 'opioid tolerant" (Component 12a, 90.3%), the survey score for Question 11 may indicate that some respondents were receiving TIRF medicine for a non-cancer associated indications..

Correct response rate for Component 10e,TIRF medicines should not be used for long-lasting pain not from cancer, like arthritis joint pain, was 43.9% for this 48-month survey. However, for Components 10a-10d, most respondents understood that TIRF medicines should not be used for headache or migraine pain (80.6%) and dental pain (90.3%); and, over half understood the TIRF medicines should not be used for pain after surgery (67.7%) and should be used for breakthrough pain from cancer (68.4%). Components 10a-10e were not included as part of a key risk message in previous surveys. In addition, correct response rate for Component 12b (*a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 39.4% in this 48-month survey.

Two of the components mentioned above with a score below the desired level of understanding of 65% for this survey (Component 10e and 12b) have had a low correct response rate across all patient/caregiver KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys); however, response rates are trending toward an increase in understanding of the use of TIRF medicines (see Table 20).

As shown in Table 20, there is a clear and consistent indication of improvement (i.e., numeric trend) in knowledge and understanding of the key risk messages. Table 20 includes key risk messages and questions/components within each key risk message as presented in the 48-month survey. It is important to note the question/component numbering, wording, and association with a specific key risk message may have changed across survey waves based on FDA feedback or other decisions made by the TRIG.

Table 20. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)
Key Risk Message 1: TIRF Medicines Can Cause Life-threatening Breathing Problems That Can Lead to Death					
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death. (*Correct Response True*)	90.1 (85.0, 93.9)	90.1 (86.1, 93.2)	91.3 (86.8, 94.6)	91.9 (88.3 - 94.7)
Key Risk Message 2: Patients Should Not Take TIRF Medicines if They Are Not Opioid Tolerant					
11/12	Please answer True, False, or I don't know for the following statement:				
11	TIRF medicines should only be taken by cancer patients who are opioid tolerant (*Correct Response True*) [2]	90.6 (85.6, 94.3)	91.7 (88.0, 94.6)	85.2 (79.9, 89.5)	43.5 (38.0 - 49.3)
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines. (*Correct Response True*)	91.7 (86.8, 95.2)	88.4 (84.3, 91.8)	81.7 (76.0, 86.5)	90.3 (86.5 - 93.4)
Key Risk Message 3: TIRF Medicines Should Be Taken Exactly as Prescribed By the Healthcare Provider					
10	For which of the following conditions should you use a TIRF medicine?				
10a	Headache or migraine pain. (*Correct Response No*)	72.9[2]	77.5[2]	78.2[2]	80.6 (75.8 - 84.9)

Table 20. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)
10b	Breakthrough pain from cancer. (*Correct Response Yes*)	69.8[2]	64.2[2]	65.9[2]	68.4 (62.9 - 73.5)
10c	Dental pain. (*Correct Response No*)	89.6[2]	87.4[2]	87.3[2]	90.3 (86.5 - 93.4)
10d	Pain after surgery. (*Correct Response No*) [2]	67.7[2]	68.5[2]	70.3[2]	67.7 (62.2 - 72.9)
10e	Long-lasting pain not from cancer, like arthritis joint pain *(Correct Response No)* [2]	24.5[2]	21.9[2]	25.3[2]	43.9 (38.3 - 49.6)
12	Please answer True, False, or I don't know for each of the following statements.				
12b	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine. (*Correct Response True*) [2]	42.7 (35.6, 50.0)	34.1 (28.8, 39.8)	36.7 (30.4, 43.3)	39.4 (33.9 - 45.0)
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b	It is OK for patients to take TIRF medicines for headache pain. (*Correct Response False*)	70.8 (63.9, 77.2)	68.2 (62.6, 73.4)	69.4 (63.0, 75.3)	74.8 (69.6 - 79.6)
13c	TIRF medicines should be taken exactly as prescribed by the doctor. (*Correct Response True*)	100.0 (98.1, 100.0)	99.7 (98.2, 100.0)	99.1 (96.9, 99.9)	100.0 (98.8 - 100.0)

Table 20. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days. (*Correct Response False*)	82.3 (76.1, 87.4)	83.4 (78.8, 87.5)	83.0 (77.5, 87.6)	86.1 (81.8 - 89.8)
Key Risk Message 4: Patients Should Not Switch From a TIRF Medicine to Another Medicine That Contains Fentanyl Without Talking to a Healthcare Provider					
12	Please answer True, False, or I don't know for each of the following statements.				
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first. (*Correct Response False*)	96.9 (93.3, 98.8)	94.4 (91.1, 96.7)	96.9 (93.8, 98.8)	95.2 (92.1 - 97.3)
Key Risk Message 5: Patients Should Never Give TIRF Medicines to Anyone Else Even if They Have the Same Symptoms					
12	Please answer True, False, or I don't know for each of the following statements.				
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient. *(Correct Response False)*	100.0 (98.1, 100.0)	98.0 (95.7, 99.3)	99.1 (96.9, 99.9)	99.4 (97.7 - 99.9)
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a	Selling or giving away TIRF medicines is against the law. *(Correct Response True)*	97.9 (94.8, 99.4)	98.3 (96.2, 99.5)	99.1 (96.9, 99.9)	98.7 (96.7 - 99.6)

Table 20. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)
Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed					
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a	TIRF medicines should be stored in a safe place out of the reach of children. *(Correct Response True)*	100.0 (98.1, 100.0)	100.0 (98.8, 100.0)	99.1 (96.9, 99.9)	99.7 (98.2 - 100.0)
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide. *(Correct Response True)*	95.8 (92.0, 98.2)	94.4 (91.1, 96.7)	93.9 (90.0, 96.6)	96.5 (93.7 - 98.2)
17e	A TIRF medicine can cause an overdose and death in any child who takes it. *(Correct Response True)*	90.6 (85.6, 94.3)	91.1 (87.3, 94.0)	90.4 (85.8, 93.9)	93.2 (89.8 - 95.8)
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.) *(Correct Response: Get emergency help right away.)*	89.1 (83.8, 93.1)	87.4 (83.1, 90.9)	88.2 (83.3, 92.1)	88.1 (83.9 - 91.5)

[1] Questions presented have been changed from previous survey waves.

[2] 95% confidence interval is not provided since the component was not part of a key risk message during reporting period.

Conclusions

In general, there is an overall trend over time toward maintenance or improvement in patient knowledge and understanding of the key risk messages (Table 20). Patients scored consistently low on two of 19 components: that TIRF medicines should not be taken for long-lasting pain not from cancer, like arthritis joint pain, and that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine. In addition, revising Question 11 (TIRF medicines should only be taken by patients who are opioid tolerant) to be specific to 'cancer' patients, resulted in a large decrease in correct response rate, which may indicate that some respondents were receiving TIRF medicine for a non-cancer associated indications. The consistently high level of patient understanding of key risk messages in the latest (48-month) survey indicates that the goals of the TIRF REMS Access Program are being met with existing tools. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

Appendix A Patient Survey Protocol Track Change Document: Comparison of 36-month Survey to 48-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Actavis Laboratories FL, Inc.** **BioDelivery Sciences International, Inc. (BDSI)** ***(replaced Meda Pharmaceuticals on March 11, 2015)*** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **Galena Biopharma, Inc.** **Insys Therapeutics, Inc.** **Mallinckrodt Pharmaceuticals** ~~***Meda Pharmaceuticals***~~ **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**10~~7~~.0**
DATE:	**13AUG2015~~18MAY2014~~**
APPROVED:	**FINAL~~Final~~**

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LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KAB	Knowledge, Attitudes, and Behavior
PBM	Pharmacy Benefits Management
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics, which are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI) (replaced Meda Pharmaceuticals on March 11, 2015); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc; Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS 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 include~~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

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the product-specific Medication Guide. This protocol will describe the administration of the surveys that will be conducted among patients who are treated with TIRF medicines, or their caregivers. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients around the following key information and risk messages communicated through the REMS:

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~~a~~ TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5) Patients should never~~not~~ 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 survey will also include questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Qualitative Research on the Survey

Qualitative research to test patient comprehension was performed on the patient survey in 2012. Findings were incorporated into the survey prior to implementation of Wave 1.

4.2 Survey Design

This survey will be conducted among a sample of patients or their caregivers who have filled a prescription for a TIRF medicine within the past 4 months (120 days) prior to survey launch. Respondents who have participated in a previous wave of the TIRF REMS KAB Survey~~survey~~ will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website
- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix B is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

4.2.1 Questions and Statements on REMS Goals

The questionnaire is made up of multiple-choice, closed-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and open-ended questions. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3. The survey is written to follow principles of health literacy and readability.

Questionnaire items will be presented in several formats:

- Statements or questions asking the respondent to indicate whether the statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes," "no," or "I don't know" as potential response options);
- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- Questions allowing for the respondent to provide information about when, where and from whom they obtained a Medication Guide, as well as to list questions they have about information in the Medication Guides.

Questionnaires will be analyzed to determine patient understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire

(Appendix A). For better readability, the patient questions, only, are presented in the key risk messages tables. Caregiver questions are presented in Appendix A.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired Responseresponse**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired Responseresponse**
11	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by cancer patients who are opioid tolerant.	**TRUE**
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**
~~**13**~~	~~Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.~~	
~~**13b**~~	~~It is OK for patients to take TIRF medicines for headache pain.~~	~~**FALSE**~~

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired Responseresponse**
10	For which of the following conditions should you use a TIRF medicine?	
10a	Headache or migraine pain	**NO**
10b	Breakthrough pain from cancer	**YES**
10c	Dental pain	**NO**
10d	Pain after surgery	**NO**
10e	Long-lasting pain not from cancer, like arthritis joint pain	**NO**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	A~~If a~~ patient must stop taking their TIRF medicine if they stop taking their ~~stops taking~~ around-the-clock opioid pain medicine~~, they must also stop taking the TIRF medicine~~.	**TRUE**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
13b	It is OK for patients to take TIRF medicines for headache pain.	**FALSE**
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**

Key Risk Message 4: Patients should not switch from one~~a~~ TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired Responseresponse**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**

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Key Risk Message 5: Patients should never~~not~~ give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired Response~~response~~**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	**TRUE**

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired Response~~response~~**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**Get emergency help right away.**

4.2.2 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and PPAF will be asked after the key risk message questions, and will be followed by the collection of demographic information at the completion of the survey.

4.3 Subject Recruitment

A random sample of patients who are passively enrolled in the TIRF REMS Access Program and have received a TIRF medicine in the previous 4 months (120 days) will be invited to participate via an invitation letter. Address verification is required on these data due to the limited data points collected through the PPAF. In order to obtain this additional information a public records database will be used and those data combined with the TIRF REMS Access Program data will be used to distribute those invitations to the select patient population. Additional patients will be identified for participation through~~Patients will be recruited through a direct letter program. Patients will be invited through a network of national pharmacies and/or~~ a pharmacy benefits management (PBM) partner, which will provide a broad demographic coverage and include patients in 49 states. Through use~~Leveraging one or more~~ of these sources~~partners~~, a list will be created of patients who have filled a prescription for a TIRF medicine within 4 months (120 days) prior to survey launch (first prescriptions and refills). Patients in this list will be invited to participate in the survey through an invitation letter (Appendix B). The letter will be sent from the Survey Coordinating Center and~~)~~ mailed directly to the patients on UBC letterhead (for the patients being invited by way of the TIRF REMS Access Program database and the public record database)~~the pharmacy~~ or the PBM's letterhead at the corporate level (for those patients being recruited through the PBM). Both invitation letters will be mailed via the United States (US) Postal Service.

The invitation will indicate that participants will receive a $50 gift card for completing the survey. Each invitation will also include a unique code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. The unique code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.

A sample of patients who have filled a prescription for a TIRF medicine within the 4 months (120 days) prior to survey launch will be chosen from the TIRF REMS Access Program database~~pharmacy partner's~~ and/or PBM's database. This sampling approach will be used to create several batches of survey invitations. The overall number of unique patients and the duration of the survey period will dictate the size and number of invitation batches. If the required number of completed surveys is not achieved within a reasonable time frame, a second mailing will be sent to non-respondents from the original batch mailing and initial invitations will be sent to patients in the second batch. If the required number of completed surveys is still not achieved within a reasonable time frame, reminder letters will be sent to the patients in the second batch and initial invitations will be sent to the third batch of patients. If these efforts do not result in the required number of surveys within a reasonable time frame, then a new sample of patients may be selected if available. The intervals for sending reminder invitations to non-responders and for selecting a new sample will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

All respondents who complete the survey and who provide their contact information will be mailed a $50 gift card to thank them for their participation. The mailing will include a thank

you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

4.3.1 Measures to Minimize Bias in the Sample

The sample of participating patients will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of patients for participation.

Respondents will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 patients treated with TIRF medicines is proposed for the survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each key risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

The following respondents are eligible to participate in the survey:

- Patients who are 18 years of age or older who have filled a prescription for at least one of the TIRF medicines within 4 months (120 days) prior to survey launch
- Caregivers 18 years of age or older who care for patients who have filled a TIRF medicine prescription within the past 4 months (120 days) prior to survey launch and are unable to take the survey for themselves

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Patients who have previously participated in the TIRF REMS KAB survey (this exclusion applies to the second and subsequent waves only)
- Patients or their immediate family members who have ever worked for Actavis Laboratories FL, Inc., Anesta LLC, BioDelivery Sciences International, Inc. (BDSI), ~~Anesta LLC,~~ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma; Insys Therapeutics, Inc.; ~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm patient eligibility. The entire survey is expected to take approximately 20 minutes to complete. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, respondents are immediately notified with a thank you message that survey participation has ended. If eligible, respondents are allowed to continue survey participation.

The electronic data capture (EDC) system that is used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient-identifying information will be stored separately from survey data.

6.1.1 Telephone

The telephone survey is facilitated by a trained interviewer from the Survey Coordinating Center using a CATI program. The respondent will be required to provide a unique code to access the survey. Working from a CATI script, the interviewer will read questions or statements to the respondent and enter the responses into the EDC system. Screening and main elements of the questionnaire will be administered sequentially during the same telephone call. Telephone interviewing allows participation of respondents who do not have Internet access, or prefer to complete the survey in this manner.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If respondents select to participate in the survey online, they will be directed to a secured website and instructed to enter a unique code to access the survey. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. Any free text fields will be grouped into applicable categories. Verbatim text from open-ended questions will be displayed when appropriate. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed all questions presented to them
- Description of survey participants, including:
  - Type of respondent (patient/caregiver)
  - Age (patient/caregiver)
  - Gender (respondent)
  - Educational level (respondent)
  - Main language spoken at home (respondent)
  - Ethnicity (respondent)
  - Race (respondent)
  - Geographic region (respondent)
- Data from all respondents who completed all questions presented to them in the survey ("completers") will be analyzed, including:
  - Frequency distribution of responses to each key risk message question.
  - Percent of completers selecting desired response to each question relating to each key risk message and 95% CI.

Measurement of understanding will be computed for each question of the key risk message individually. A secondary analysis will be conducted to determine the number of completers who answered all items correctly for the key risk message. Behavior questions will be summarized on a question-by-question basis and are not included in the analysis by key risk message.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The survey will be conducted via the Internet and by telephone. It is possible that a respondent may report an adverse event or other safety event experienced while taking TIRF medicines either in free text fields of the survey or while in conversation with the Survey Coordinating Center. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. The respondent will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact him/her if there are questions about the survey. The Internet-based questionnaires will be monitored for any comments recorded in free text fields. Information on all comments that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail a $50 gift card, a Thank You Letter, a product-specific Medication Guide, and correct survey responses to key risk message questions after the survey is completed. Respondent contact information is also requested in the event a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information. A respondent may be contacted only if clarification or follow-up is needed regarding a possible safety event that was mentioned to the interviewer or recorded in free text fields of the online survey.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to receive TIRF medicines.

This protocol and survey will be reviewed and approved by a central Institutional Review Board (IRB) before administration of the survey.

APPENDIX A Screening and Main Questionnaire

Survey Legend

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- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.
- **[PATIENT]** indicates text applicable to a patient when it differs from survey text for caregivers, parents and legal guardians.
- **[OTHER~~[PARENT/CAREGIVER/LEGAL GUARDIAN]~~]** indicates text applicable to parents, caregivers, and legal guardians when it differs from survey text for patients.
- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone~~telephone~~ only (for example, spontaneous adverse event reporting).
- **[ONLINE]** indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.
- **[BEGIN ~~ONLINE/PHONE~~ SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.
- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.
- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.
- **[GO TO Qx~~Ax~~]** (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to

Survey Legend

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question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

- Response options for questions that allow multiple responses must be indicated with check boxes (□). At least one option must be selected for the question to be considered answered.
- If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option.

- Response options for questions that allow only one response must be indicated with radio buttons (○).
- If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.

- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.

- ~~**[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.~~

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- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

Survey Legend

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- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
- West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

Survey Legend

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

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[BEGIN SURVEY CONTENT]

[BEGIN ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by UBC on behalf of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program ("TIRF REMS Access Program" or Program), sponsors of which include the makers of Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys® and the generic versions of any of these brands. These TIRF Medicines are~~are Transmucosal Immediate Release Fentanyl medicines,~~ also known as rapid onset opioids (and sometimes called "fast acting fentanyls"). Please note that references to the TIRF REMS Access Program in this introduction include the sponsors of the Program, as well as its retained agents or contractors, including UBC.") ~~or TIRF medicines.~~

The information collected will help the makers of TIRF Medicines~~medicines~~ know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF Medicines~~medicines~~.

How We Use Your Information

The terms of the TIRF REMS Access Program Patient-Prescriber Agreement Form (PPAF) on file and the Patient Privacy Notice contained therein, provide that the TIRF REMS Access Program may receive, use, and share your health information, using a unique identifier instead of your name, in order to evaluate the proper use of TIRF Medicines and report to the Food and Drug Administration (FDA) about the effectiveness of the Program. Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used or shared with the TIRF REMS Access Program according to these terms.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be collected by UBC, compiled~~put together~~ and reported in anonymous form to the~~manufacturers of~~ TIRF REMS Access Program and the FDA~~medicines~~. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be received only by UBC and will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

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How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. The ~~Neither the manufacturers of~~ TIRF REMS Access Program~~medicines nor their contractors~~ will not sell, transfer (except in connection with reporting to the FDA),~~.~~ or rent your information. ~~Your answers will be kept strictly confidential.~~ Your privacy will be protected; however, research survey records may be inspected by the FDA ~~(Food and Drug Administration)~~ and a company called (b) (4)., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the ~~manufacturers of~~ TIRF REMS Access Program~~medicines~~ to use your information is entirely voluntary, but necessary to take part in this survey.

Please be assured that your contact information and your individual responses will be kept strictly confidential. As noted above, however, information you provide will be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be used by the TIRF REMS Access Program and disclosed to the FDA. By participating, you also acknowledge that the FDA and/or IRB, may inspect the records related to this survey which may include your individual responses.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4). Be sure to write down this telephone number; it will not be displayed again.

How to Learn More About This Survey

If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF Medicines~~medicines~~, talk to your doctor, pharmacist, or other health care professional.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

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[BEGIN PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by UBC on behalf of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program ("TIRF REMS Access Program" or Program) sponsors of which include the makers of Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys® and the generic versions of any of these brands. These TIRF Medicines~~are Transmucosal Immediate Release Fentanyl medicines~~, also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** (and sometimes called "fast acting fentanyls") or TIRF Medicines. Please note that references to the TIRF REMS Access Program in this introduction include the sponsors of the Program, as well as its retained agents or contractors, including UBC ~~medicines.~~

(INTERVIEWER: Pronounce "TIRF," then spell out T-I-R-F).

The information collected will help the makers of TIRF Medicines~~medicines~~ know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF Medicines~~medicines~~.

Now I would like to tell you about how your contact information will be used.

The terms of the TIRF REMS Access Program Patient-Prescriber Agreement Form (PPAF) on file and the Patient Privacy Notice contained therein, provide that the TIRF REMS Access Program may receive, use, and share your health information, using a unique identifier instead of your name, in order to evaluate the proper use of TIRF Medicines and report to the Food and Drug Administration (FDA) about the effectiveness of the Program. Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used or shared with the TIRF REMS Access Program according to these terms.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be collected by UBC, compiled,~~put together~~ and reported in anonymous form to the~~manufacturers of~~ TIRF REMS Access Program and the FDA~~medicines~~. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be received only by UBC and will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

Now I would like to tell you about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. The ~~Neither the manufacturers of~~ TIRF REMS Access Program~~medicines nor their contractors~~ will not sell, transfer (except in connection with reporting to the FDA),~~,~~ or rent your information. ~~Your answers will be kept strictly confidential.~~ Your privacy will be protected; however, research survey records may be inspected by the FDA ~~(Food and Drug Administration)~~ and a company called (b) (4)., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the ~~manufacturers of~~ TIRF REMS Access Program~~medicines~~ to use your information is entirely voluntary, but necessary to take part in this survey.

Please be assured that your contact information~~,~~ and your individual responses will be kept strictly confidential. As noted above, however, information you provide will be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be used by the TIRF REMS Access Program and disclosed to the FDA. By participating, you also acknowledge that the FDA and/or IRB, may inspect the records related to this survey which may include your individual responses.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at (b) (4)

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF Medicines~~medicines~~, talk to your doctor, pharmacist, or other health care professional.

Please feel free to ask me to repeat any questions or statements as we go through the survey.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 4 months (120 days), have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®, and the generic versions of any of these brands.

   - ○ Yes **[GO TO Q4]**
   - ○ No
   - ○ I don't know

3. Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months (120 days)? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys® and the generic versions of any of these brands.

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. **[PATIENT]** For which TIRF medicines have you filled a prescription in the last 4 months (120 days)?~~?~~ Please select all that apply.

[CAREGIVER] For which TIRF medicines has the person you care for filled a prescription in the last 4 months (120 days)?~~?~~ Please select all that apply.

- □ Abstral
- □ Actiq, including generic versions of Actiq
- □ Fentora
- □ Lazanda
- ~~□ Onsolis~~
- □ Subsys
- □ Other
- □ I don't know **[CLEAR ALL OTHER SELECTIONS]**

5. Have you ever taken part in a survey about a TIRF medicine before?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

6. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE]**
- ○ 18 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

7. **[CAREGIVER ~~ONLY~~]** Which of the following groups best describes the patient's age?

- ○ Under 16
- ○ 16 – 29
- ○ 30 – 39
- ○ 40 – 49
- ○ 50 – 59
- ○ 60 – 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

8. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- ☐ Actavis Laboratories FL, Inc. **[TERMINATE]**
- ☐ Anesta LLC **[TERMINATE]**
- ☐ BioDelivery Services International (BDSI) **[TERMINATE]**
- ☐ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
- ☐ Depomed, Inc. **[TERMINATE]**
- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics, Inc. **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ~~☐~~ ~~Meda Pharmaceuticals **[TERMINATE]**~~
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth**[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA (Food and Drug Administration) **[TERMINATE]**
- ☐ No **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

[BEGIN

[PREAMBLE 2 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

[BEGIN PATIENT] Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for you. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[END PATIENT]

[BEGIN CAREGIVER] Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for the patient. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you or to the patient by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[END CAREGIVER]

[END PREAMBLE 2]

9. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and the generic versions of these brands.

   [CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed to the patient? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and the generic versions of these brands.

   - o Yes
   - o No
   - o I don't know

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10. **[PATIENT]** For which of the following conditions should you use a TIRF medicine?

[CAREGIVER] For which of the following conditions should the person you take care of use a TIRF medicine?

[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
10a. Headache or migraine pain	○	○	○
10b. Breakthrough pain from cancer	○	○	○
10c. Dental pain	○	○	○
10d. Pain after surgery	○	○	○
10e. Long-lasting pain~~painful conditions~~ not from~~caused by~~ cancer, like arthritis joint pain	○	○	○

11. Please answer True, False, or I don't know for the following statement:

TIRF medicines should only be taken by cancer patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

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

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[RANDOMIZE LIST]	**True**	**False**	**I don't know**
12a. Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	○	○	○
12b. A~~If a~~ patient must stop taking their TIRF medicine if they stop taking their ~~stops taking~~ around-the-clock opioid pain medicine~~, they must also stop taking the TIRF medicine~~.	○	○	○
12c. It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	○	○	○

12d.	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	○	○	○

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

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
13a. TIRF medicines should be stored in a safe place out of the reach of children.	○	○	○
13b. It is OK for patients to take TIRF medicines for headache pain.	○	○	○
13c. TIRF medicines should be taken exactly as prescribed by the doctor.	○	○	○
13d. TIRF medicines can cause life-threatening breathing problems that can lead to death.	○	○	○

14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- ○ Wait an hour and see if the person is OK.
- ○ Get emergency help right away.
- ○ Do nothing.
- ○ I don't know.

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15. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

16. **[PATIENT]** Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for the patient?

- o Yes
- o No
- o I don't know

17. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
17a. Selling or giving away TIRF medicines is against the law.	○	○	○
17b. It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
17c. TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
17d. TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access Program).	○	○	○
17e. A TIRF medicine can cause an overdose and death in any child who takes it.	○	○	○

[BEGIN PREAMBLE 3 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

[BEGIN PATIENT] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for you.

[END PATIENT]

[BEGIN ~~[~~CAREGIVER] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for the patient.

[END CAREGIVER]

~~[BOTH]~~ A Medication Guide is a paper handout that contains important information about the risks associated with the use of a TIRF medicine and how to use it safely. Medication Guides always include the title "Medication Guide" followed by the name of the medicine and its pronunciation. The Medication Guide usually has a section titled "What is the most important information I should know?" The Medication Guide is in a question-and-answer format and may be given to you by your pharmacist, doctor, or other healthcare professional.

[END PREAMBLE 3]

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18. **[PATIENT]** Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?

[CAREGIVER] Have you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for the patient?

- ○ Yes
- ○ No **[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

19. **[PATIENT]** Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

[CAREGIVER] Did you or the patient receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

- ○ Yes
- ○ No **[GO TO Q21]**
- ○ I don't know **[GO TO Q21]**

20. **[PATIENT]** When was the Medication Guide given to you? Please select all that apply.

[CAREGIVER] When was the Medication Guide given to you or the patient? Please select all that apply.

- □ At the first appointment with the doctor who prescribed the TIRF medicine
- □ At the last appointment with the doctor who prescribed the TIRF medicine
- □ I don't remember **[CLEAR ALL OTHER SELECTIONS]**

21. **[PATIENT]** Did you receive the Medication Guide for the TIRF medicine from the pharmacy?

[CAREGIVER] Did you or the patient receive the Medication Guide for the TIRF medicine from the pharmacy?

- ○ Yes
- ○ No **[GO TO Q23]**
- ○ I don't know **[GO TO Q23]**

22. **[PATIENT]** How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] How frequently do you or the patient receive a Medication Guide for the TIRF medicine at the pharmacy?

- ○ Only with the first filled prescription
- ○ Each time a prescription is filled
- ○ Other (please specify): **[FREE TEXT]**
- ○ I don't know

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23. Did you read the Medication Guide?

- ○ Yes
- ○ No **[GO TO Q26]**
- ○ I don't know **[GO TO Q26]**

24. How much did you read?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ I don't know

25. How much of the Medication Guide did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

26. Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

27. Who offered to explain the Medication Guide to you? Please select all that apply.

- □ The doctor or another healthcare professional in the doctor's office
- □ The pharmacist where the TIRF medicine prescription was filled
- □ Someone else **[IF SELECTED, SHOW THE FOLLOWING ON THE SAME PAGE:]**

  Specify~~(specify~~ the type of person but not his/her name:~~)~~

  [FREE TEXT]

28. Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO Q30]**
- ○ I don't know **[GO TO Q30]**

29. How much of the explanation did you understand?

- All of it
- Most of it
- Some of it
- None of it
- I don't know

30. Did you or do you have any questions about the information in the Medication Guide?

- Yes
- No **[GO TO PREAMBLE 4]**
- I don't know **[GO TO PREAMBLE 4]**

[IF QUESTION 30 = YES, DISPLAY Q31 ON SAME PAGE]

31. What are your questions? **[MULTILINE INPUT]**

[BEGIN PREAMBLE 4 – DISPLAY ON SAME PAGE AS NEXT QUESTION]

The next set of questions is about the Patient-Prescriber Agreement Form for TIRF medicines. As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys®, and the generic versions of any of these brands. The Patient-Prescriber Agreement is a form that is signed by the doctor and the patient or their caregiver. This form may also be referred to as the Prescriber-Patient Agreement.

[END PREAMBLE 4]

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32. Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- ○ Yes
- ○ No **[GO TO Q34]**
- ○ I don't know **[GO TO Q34]**

33. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

34. **[PATIENT]** Did you sign a Patient-Prescriber Agreement Form?

[CAREGIVER] Did you or the person you are caring for sign a Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

35. Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No
- ○ I don't know

[BEGIN DEMOGRAPHICS PREAMBLE - DISPLAY ON SAME PAGE AS NEXT QUESTION]

There are just a few more questions to help us combine your answers with other answers we have received.

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[END DEMOGRAPHICS PREAMBLE]

36. What is your gender?

- Male
- Female
- Prefer not to answer

37. What is the highest level of education you have completed?

- Less than high school
- Some high school
- High school graduate/GED
- Some college/Associate's degree
- Bachelor's degree
- Master's degree
- Professional or Doctoral degree
- Prefer not to answer

38. What is the main language you speak at home?

- English
- French
- Spanish
- Portuguese
- Italian
- German
- Chinese
- Japanese
- Korean
- Other
- Prefer not to answer

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39. Are you Hispanic or Latino?

- ○ Yes
- ○ No
- ○ Prefer not to answer

40. For informational purposes only, which of the following U.S. census categories best describes your race?

- ○ American Indian or Alaska Native
- ○ Asian (origins of Far East, Southeast Asia or the Indian subcontinent)
- ○ Black or African American
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ Two or more races
- ○ Other
- ○ Prefer not to answer

41. In which state do you live?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE - BEGIN~~ONLY:~~ ADVERSE EVENT/PRODUCT COMPLAINT – KEEP ON ONE PAGE]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- Yes
- No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[BEGIN

~~[~~CLOSING 1 – KEEP ON ONE PAGE]

You are eligible to receive a $50 gift card for your time completing the survey. In order to receive the gift card, we need to collect your name and address so that we can mail it to you. If you do not provide your name and address you will not receive the gift card for your time taking the survey.

Do you agree to give us your name and mailing address so we can send your payment?

- Yes
- No **[GO~~SKIP~~ TO CLOSING 2]**

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FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: [MUST BE 5 DIGIT NUMERIC-ONLY CHARACTERS~~-ONLY~~]

[END CLOSING 1]

[BEGIN ~~(~~CLOSING 2 – KEEP ON ONE PAGE]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- ○ Yes
- ○ No [GO~~SKIP~~ TO CLOSING 3]

Telephone: [MUST BE 10-DIGIT NUMERIC-ONLY CHARACTERS]

[END CLOSING 2]

[BEGIN CLOSING 3]

This is the end of the survey. If you have questions about the survey, please contact the Survey Coordinating Center at 1-877-379-3297. ~~-~~Thank you again for your help.

[END CLOSING 3]

[END~~OF~~ SURVEY CONTENT]

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APPENDIX B SAMPLE Patient Letter of Invitation

[PAT_FIRST_NAME] [PAT_LAST_NAME
[CURR_DATE]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

Thank you for choosing [pharmacy partner or PBM name] for your prescription needs. The purpose of this letter is to inform you about a voluntary research survey being conducted by [COMPANY], the maker of [BRAND_GENERIC]. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about [BRAND] and other medicines like it. The first 300 people who complete this 20-minute survey and provide their contact information will receive a $50 [pharmacy partner or PBM name] gift card from [COMPANY] to thank them for their time.

You may be eligible to take part if you have taken [BRAND] and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about [BRAND] and where you get your medical information.

If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

It is recommended that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

(over, please)

You are not required to take part in this survey. If you choose to take part, please be assured that your contact information and your individual responses will be kept strictly confidential. You will not be asked to identify yourself to participate in the survey. However, if you wish to receive the $50 gift card from [COMPANY], you must provide your name and contact information for delivery. Your answers to the survey questions will be combined with answers given by others, and your name will not be used in any written report or publication. Neither taking the survey nor your answers to the questions will affect your ability to receive or take [BRAND].

Sincerely,

[Pharmacy partner or PBM name]

[COMPANY] funded the cost of the gift card, the cost of mailing this letter and paid a fee to [pharmacy partner or PBM name]. The research study is not being conducted by [pharmacy partner or PBM name]. No information that can identify you, your medication, or your health condition will be provided by [pharmacy partner or PBM name] to [COMPANY]. This letter provides information about a drug prescribed by your doctor and is not a recommendation by [pharmacy partner or PBM name] to use a particular drug for your condition. Call [pharmacy partner or PBM name] toll free at xxx-xxx-xxxx if you do not wish to continue receiving mailings about [BRAND] from [pharmacy partner or PBM name].

Appendix B Patient Survey Listings and Stratified Analyses Tables

Table 1.1: Survey Administration Statistics

Parameter, n (%)	
Number of invitations distributed	5569
Number of invitations returned as undeliverable	148
Number of reminder letters distributed	447
All Respondents[1]	432 (8.0)
Eligible Respondents[2]	314 (72.7)
Completed survey[3]	310 (98.7)
Did not complete the survey[3]	4 (1.3)
Respondents not eligible[2][4]	118 (27.3)

[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentages are based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Patients/Caregivers (N=432) n (%)
Question 1: Do you agree to take part in this survey?	
Yes	373 (86.3)
No[1]	1 (0.2)
Discontinued	58 (13.4)
Question 2: Within the last 4 months (120 days), have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of any of these brands.	
Yes	352 (81.5)
No	14 (3.2)
I don't know	6 (1.4)
Question not asked [2]	1 (0.2)
Discontinued	59 (13.7)
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months (120 days)? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands.	
Yes	4 (0.9)
No[1]	15 (3.5)
I don't know[1]	1 (0.2)
N/A *(Answered "Yes" to Question 2)*	352 (81.5)
Question not asked [2]	1 (0.2)
Discontinued	59 (13.7)
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months (120 days)? Please select all that apply.	
Abstral	15 (3.5)
Actiq, including generic versions of Actiq	127 (29.4)
Fentora	66 (15.3)
Lazanda	19 (4.4)
Subsys	146 (33.8)
Other	15 (3.5)
I don't know	1 (0.2)

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Patients/Caregivers (N=432) n (%)
Question not asked [2]	17 (3.9)
Discontinued	59 (13.7)
Question 5: Have you ever taken part in a survey about a TIRF medicine before?	
Yes[1]	29 (6.7)
No	315 (72.9)
I don't know[1]	12 (2.8)
Question not asked [2]	17 (3.9)
Discontinued	59 (13.7)
Question 6: Which of the following groups best describes your age?	
Under 18[1]	0
18 - 29	5 (1.2)
30 - 39	20 (4.6)
40 - 49	66 (15.3)
50 - 59	132 (30.6)
60 - 69	76 (17.6)
70 or older	16 (3.7)
Prefer not to answer[1]	0
Question not asked [2]	58 (13.4)
Discontinued	59 (13.7)
Question 7: Which of the following groups best describes the patient's age?[3]	
Under 16	0
16 - 29	0
30 - 39	0
40 - 49	1 (0.2)
50 - 59	0
60 - 69	2 (0.5)
70 or older	1 (0.2)
Prefer not to answer[1]	0

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Patients/Caregivers (N=432) n (%)
Question not asked [2]	369 (85.4)
Discontinued	59 (13.7)
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.	
Actavis Laboratories FL, Inc.[1]	0
Anesta LLC[1]	0
BioDelivery Services International (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd.)[1]	1 (0.2)
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	0
Mallinckrodt Pharmaceuticals[1]	0
McKesson Specialty Care Solutions[1]	0
Mylan, Inc.[1]	0
Par Pharmaceutical, Inc.[1]	0
RelayHealth[1]	0
Teva Pharmaceuticals, Ltd.[1]	0
United BioSource Corporation[1]	0
FDA (Food and Drug Administration)[1]	0
No[4]	314 (72.7)
I don't know[1]	0
Question not asked [2]	58 (13.4)
Discontinued	59 (13.7)

[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question or skip pattern.
[3] Only caregivers are asked this question.
[4] Ineligible to participate in the survey if selected in addition to other responses.
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

Table 1.3: Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total
Summary Statistic (minutes)			
N	116	194	310
Mean (SD)	21.69 (9.062)	14.42 (8.677)	17.14 (9.487)
Minimum	14.1	4.5	4.5
Median	19.61	12.81	16.47
Maximum	102.3	85.8	102.3
Category, n			
0 to <5 Minutes	0	2	2
5 to <10 Minutes	0	52	52
10 to <15 Minutes	1	81	82
15 to <20 Minutes	68	30	98
20 to <25 Minutes	31	12	43
25 to <30 Minutes	7	9	16
30 Minutes or more	9	8	17

Table 2: Description and Representativeness of Eligible Patients/Caregivers - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
Respondent's age based on Question 6: Which of the following groups best describes your age?	
18 - 29	5 (1.6)
30 - 39	19 (6.1)
40 - 49	65 (21.0)
50 - 59	129 (41.6)
60 - 69	76 (24.5)
70 or older	16 (5.2)
Patient's age based on Question 6/7: Which of the following groups best describes your age/the patient's age?	
Under 16	0
16 - 29	5 (1.6)
30 - 39	19 (6.1)
40 - 49	65 (21.0)
50 - 59	128 (41.3)
60 - 69	77 (24.8)
70 or older	16 (5.2)
Question 36: What is your gender?	
Male	133 (42.9)
Female	176 (56.8)
Prefer not to answer	1 (0.3)
Question 37: What is the highest level of education you have completed?	
Less than high school	4 (1.3)
Some high school	7 (2.3)
High school graduate/GED	48 (15.5)
Some college/Associates' degree	123 (39.7)
Bachelor's degree	71 (22.9)
Master's degree	38 (12.3)
Professional or Doctoral degree	15 (4.8)
Prefer not to answer	4 (1.3)

Table 2: Description and Representativeness of Eligible Patients/Caregivers - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
Question 38: What is the main language you speak at home?	
English	309 (99.7)
French	0
Spanish	0
Portuguese	0
Italian	0
German	0
Chinese	0
Japanese	0
Korean	0
Other	0
Prefer not to answer	1 (0.3)
Question 39: Are you Hispanic or Latino?	
Yes	9 (2.9)
No	296 (95.5)
Prefer not to answer	5 (1.6)
Question 40: For informational purposes only, which of the following U.S. census categories best describes your race?	
American Indian or Alaska Native	3 (1.0)
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	2 (0.6)
Black or African American	15 (4.8)
Native Hawaiian or Other Pacific Islander	3 (1.0)
White	265 (85.5)
Other	4 (1.3)
Prefer not to answer	11 (3.5)
Two or more races	7 (2.3)
Geographic Distribution (based on Question 41 - In which state do you live?)[1]	
Northeast	51 (16.5)
Midwest	61 (19.7)

Table 2: Description and Representativeness of Eligible Patients/Caregivers - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
South	117 (37.7)
West	81 (26.1)
Other	0
Prefer not to answer	0

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Table 2a: Comparison of Survey Respondents to General Population of TIRF Users

Question	Eligible/Completed Patients & Caregivers (N=310) n (%)	Patients Who Have Taken a TIRF Medicine in the Last 4 Months (120 days)[1] (N=9858) n (%)
Geographic Distribution[2]		
Northeast	51 (16.5)	1811 (18.4)
Midwest	61 (19.7)	1305 (13.2)
South	117 (37.7)	4021 (40.8)
West	81 (26.1)	2706 (27.4)
Other	0	0
Prefer not to answer	0	0
Missing	0	15 (0.2)

[1] Based on data obtained from the TIRF REMS Access Program database.
[2] Based on Patient KAB Survey Question 41; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
Note: Percentages are based on the patients and caregivers with informative data.

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
Question 9: Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands.	
Yes	259 (83.5)
No	36 (11.6)
I don't know	15 (4.8)
Question 10: For which of the following conditions should you use a TIRF medicine?	
10a: Headache or migraine pain	
Yes	32 (10.3)
No[1]	250 (80.6)
I don't know	28 (9.0)
10b: Breakthrough pain from cancer	
Yes[1]	212 (68.4)
No	80 (25.8)
I don't know	18 (5.8)
10c: Dental pain	
Yes	8 (2.6)
No[1]	280 (90.3)
I don't know	22 (7.1)
10d: Pain after surgery	
Yes	65 (21.0)
No[1]	210 (67.7)
I don't know	35 (11.3)
10e: Long-lasting pain not from cancer, like arthritis joint pain	
Yes	135 (43.5)
No[1]	136 (43.9)
I don't know	39 (12.6)
Question 11: Please answer True, False, or I don't know for the following statement:	
TIRF medicines should only be taken by cancer patients who are opioid tolerant.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
True[1]	135 (43.5)
False	122 (39.4)
I don't know	53 (17.1)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	
True[1]	280 (90.3)
False	14 (4.5)
I don't know	16 (5.2)
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[1]	122 (39.4)
False	93 (30.0)
I don't know	95 (30.6)
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	
True	5 (1.6)
False[1]	295 (95.2)
I don't know	10 (3.2)
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	
True	0
False[1]	308 (99.4)
I don't know	2 (0.6)
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.	
13a: TIRF medicines should be stored in a safe place out of the reach of children.	
True[1]	309 (99.7)
False	1 (0.3)
I don't know	0
13b: It is OK for patients to take TIRF medicines for headache pain.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
True	20 (6.5)
False[1]	232 (74.8)
I don't know	58 (18.7)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.	
True[1]	310 (100.0)
False	0
I don't know	0
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.	
True[1]	285 (91.9)
False	3 (1.0)
I don't know	22 (7.1)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	
Wait an hour and see if the person is OK.	6 (1.9)
Get emergency help right away.[1]	273 (88.1)
Do nothing.	1 (0.3)
I don't know.	30 (9.7)
Question 15: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?	
Yes	296 (95.5)
No	9 (2.9)
I don't know	5 (1.6)
Question 16: Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?	
Yes	255 (82.3)
No	49 (15.8)
I don't know	6 (1.9)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a: Selling or giving away TIRF medicines is against the law.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
True[1]	306 (98.7)
False	2 (0.6)
I don't know	2 (0.6)
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.	
True	13 (4.2)
False[1]	267 (86.1)
I don't know	30 (9.7)
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.	
True[1]	299 (96.5)
False	2 (0.6)
I don't know	9 (2.9)
17d: TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access Program).	
True	236 (76.1)
False	8 (2.6)
I don't know	66 (21.3)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.	
True[1]	289 (93.2)
False	2 (0.6)
I don't know	19 (6.1)

[1] Correct response.

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
Question 18: Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?	
Yes	298 (96.1)
No	7 (2.3)
I don't know	5 (1.6)
Question 19: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?[1]	
Yes	174 (58.4)
No	106 (35.6)
I don't know	18 (6.0)
N/A (Answered "No" or "I don't know" to Question 18)	12
Question 20: When was the Medication Guide given to you? Please select all that apply.[1]	
At the first appointment with the doctor who prescribed the TIRF medicine	146 (83.9)
At the last appointment with the doctor who prescribed the TIRF medicine	23 (13.2)
I don't remember	24 (13.8)
N/A (answered "No" or "I don't know" to Question 18 or 19)	136
Question 21: Did you receive the Medication Guide for the TIRF medicine from the pharmacy?[1]	
Yes	250 (83.9)
No	33 (11.1)
I don't know	15 (5.0)
N/A (Answered "No" or "I don't know" to Question 18)	12
Question 22: How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?[1]	
Only with the first filled prescription	8 (3.2)
Each time a prescription is filled	230 (92.0)
Other (please specify):[2]	3 (1.2)
I don't know	9 (3.6)
N/A (Answered "No" or "I don't know" to Question 18 or 21)	60
Question 23: Did you read the Medication Guide?[1]	
Yes	287 (96.3)

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
No	8 (2.7)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 18)	12
Question 24: How much did you read?[1]	
All of it	198 (69.0)
Most of it	75 (26.1)
Some of it	13 (4.5)
I don't know	1 (0.3)
N/A (Answered "No" or "I don't know" to Question 18 or 23)	23
Question 25: How much of the Medication Guide did you understand?[1]	
All of it	155 (54.0)
Most of it	108 (37.6)
Some of it	23 (8.0)
None of it	0
I don't know	1 (0.3)
N/A (Answered "No" or "I don't know" to Question 18 or 23)	23
Question 26: Did someone offer to explain the Medication Guide to you?[1]	
Yes	171 (57.4)
No	111 (37.2)
I don't know	16 (5.4)
N/A (Answered "No" or "I don't know" to Question 18)	12
Question 27: Who offered to explain the Medication Guide to you? Please select all that apply.[1]	
The doctor or another healthcare professional in the doctor's office	123 (71.9)
The pharmacist where the TIRF medicine prescription was filled	127 (74.3)
Someone else[3]	15 (8.8)
N/A (Answered "No" or "I don't know" to Question 18 or 26)	139
Question 28: Did you accept the offer to have the Medication Guide explained to you?[1]	
Yes	119 (69.6)

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
No	49 (28.7)
I don't know	3 (1.8)
N/A (Answered "No" or "I don't know" to Question 18 or 26)	139
Question 29: How much of the explanation did you understand?[1]	
All of it	92 (77.3)
Most of it	25 (21.0)
Some of it	2 (1.7)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 18, 26 or 28)	191
Question 30: Did you or do you have any questions about the information in the Medication Guide?[1]	
Yes[4]	16 (5.4)
No	277 (93.0)
I don't know	5 (1.7)
N/A (Answered "No" or "I don't know" to Question 18)	12

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim texts for question 22 (Other frequency of receiving a Medication Guide in the pharmacy) are presented in Listing 1.
[3] Verbatim texts for question 27 (Other type of person explaining Medication Guide) are presented in Listing 2.
[4] Verbatim texts for questions about the Medication Guide are presented in Listing 3.

Table 5: Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys

Question	Patients/Caregivers (N=310) n (%)
Question 32: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?	
Yes	256 (82.6)
No	27 (8.7)
I don't know	27 (8.7)
Question 33: How much of the explanation did you understand?[1]	
All of it	204 (79.7)
Most of it	44 (17.2)
Some of it	4 (1.6)
None of it	1 (0.4)
I don't know	3 (1.2)
N/A (Answered "No" or "I don't know" to Question 32)	54
Question 34: Did you sign a Patient-Prescriber Agreement Form?	
Yes	248 (80.0)
No	13 (4.2)
I don't know	49 (15.8)
Question 35: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?[1]	
Yes	180 (72.6)
No	27 (10.9)
I don't know	41 (16.5)
N/A (Answered "No" or "I don't know" to Question 34)	62

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines can cause life-threatening breathing problems that can lead to death.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
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.	
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.	
True[2]	285 (91.9) [88.3 - 94.7]
False	3 (1.0)
I don't know	22 (7.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys

Key Risk Message #1: TIRF medicines can cause life-threatening breathing problems that can lead to death.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
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.		
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
True[2]	177 (91.2) [86.3 - 94.8]	108 (93.1) [86.9 - 97.0]
False	3 (1.5)	0
I don't know	14 (7.2)	8 (6.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Highest Level of Education - Completed Surveys

Key Risk Message #1: TIRF medicines can cause life-threatening breathing problems that can lead to death.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
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.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True[2]	56 (88.9) [78.4 - 95.4]	113 (91.9) [85.6 - 96.0]	102 (93.6) [87.2 - 97.4]	14 (93.3) [68.1 - 99.8]
False	0	1 (0.8)	2 (1.8)	0
I don't know	7 (11.1)	9 (7.3)	5 (4.6)	1 (6.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Note: "GED or less" includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." "College" includes "Some college/Associate's degree." "BA/BS or MS/MA" includes "Bachelor's degree" and "Master's degree." "Professional or Doctoral degree" includes "Professional or Doctoral degree."

Table 6.1.5: Responses to Questions Linked to Key Risk Message #1 by Age Group of Respondent - Completed Surveys

Key Risk Message #1: TIRF medicines can cause life-threatening breathing problems that can lead to death.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
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.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True[2]	24 (100.0) [85.8 - 100.0]	59 (90.8) [81.0 - 96.5]	118 (91.5) [85.3 - 95.7]	84 (91.3) [83.6 - 96.2]
False	0	0	2 (1.6)	1 (1.1)
I don't know	0	6 (9.2)	9 (7.0)	7 (7.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #2: Patients should not take TIRF medicines if they are not opioid tolerant.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:	
TIRF medicines should only be taken by cancer patients who are opioid tolerant.	
True[2]	135 (43.5) [38.0 - 49.3]
False	122 (39.4)
I don't know	53 (17.1)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	
True[2]	280 (90.3) [86.5 - 93.4]
False	14 (4.5)
I don't know	16 (5.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys

Key Risk Message #2: Patients should not take TIRF medicines if they are not opioid tolerant.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:		
TIRF medicines should only be taken by cancer patients who are opioid tolerant.		
True[2]	94 (48.5) [41.2 - 55.7]	41 (35.3) [26.7 - 44.8]
False	75 (38.7)	47 (40.5)
I don't know	25 (12.9)	28 (24.1)
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.		
True[2]	179 (92.3) [87.6 - 95.6]	101 (87.1) [79.6 - 92.6]
False	8 (4.1)	6 (5.2)
I don't know	7 (3.6)	9 (7.8)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Highest Level of Education - Completed Surveys

Key Risk Message #2: Patients should not take TIRF medicines if they are not opioid tolerant.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by cancer patients who are opioid tolerant.				
True[2]	25 (39.7) [27.6 - 52.8]	51 (41.5) [32.7 - 50.7]	52 (47.7) [38.1 - 57.5]	7 (46.7) [21.3 - 73.4]
False	26 (41.3)	51 (41.5)	39 (35.8)	6 (40.0)
I don't know	12 (19.0)	21 (17.1)	18 (16.5)	2 (13.3)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True[2]	51 (81.0) [69.1 - 89.8]	112 (91.1) [84.6 - 95.5]	104 (95.4) [89.6 - 98.5]	13 (86.7) [59.5 - 98.3]
False	4 (6.3)	7 (5.7)	1 (0.9)	2 (13.3)
I don't know	8 (12.7)	4 (3.3)	4 (3.7)	0

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Note: "GED or less" includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." "College" includes "Some college/Associate's degree." "BA/BS or MS/MA" includes "Bachelor's degree" and "Master's degree." "Professional or Doctoral degree" includes "Professional or Doctoral degree."

Table 7.1.5: Responses to Questions Linked to Key Risk Message #2 by Age Group of Respondent - Completed Surveys

Key Risk Message #2: Patients should not take TIRF medicines if they are not opioid tolerant.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by cancer patients who are opioid tolerant.				
True[2]	14 (58.3) [36.6 - 77.9]	27 (41.5) [29.4 - 54.4]	60 (46.5) [37.7 - 55.5]	34 (37.0) [27.1 - 47.7]
False	8 (33.3)	30 (46.2)	47 (36.4)	37 (40.2)
I don't know	2 (8.3)	8 (12.3)	22 (17.1)	21 (22.8)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True[2]	23 (95.8) [78.9 - 99.9]	59 (90.8) [81.0 - 96.5]	120 (93.0) [87.2 - 96.8]	78 (84.8) [75.8 - 91.4]
False	1 (4.2)	2 (3.1)	4 (3.1)	7 (7.6)
I don't know	0	4 (6.2)	5 (3.9)	7 (7.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #2: Patients should not take TIRF medicines if they are not opioid tolerant.

Correct Responses	Patients/Caregivers (N=310) n (%) [95% CI][1]
0 correct responses	24 (7.7)
1 correct response	157 (50.6)
2 correct responses	129 (41.6) [36.1 - 47.3]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine?	
10a: Headache or migraine pain	
Yes	32 (10.3)
No[2]	250 (80.6) [75.8 - 84.9]
I don't know	28 (9.0)
10b: Breakthrough pain from cancer	
Yes[2]	212 (68.4) [62.9 - 73.5]
No	80 (25.8)
I don't know	18 (5.8)
10c: Dental pain	
Yes	8 (2.6)
No[2]	280 (90.3) [86.5 - 93.4]
I don't know	22 (7.1)
10d: Pain after surgery	
Yes	65 (21.0)
No[2]	210 (67.7) [62.2 - 72.9]
I don't know	35 (11.3)
10e: Long-lasting pain not from cancer, like arthritis joint pain	
Yes	135 (43.5)
No[2]	136 (43.9) [38.3 - 49.6]
I don't know	39 (12.6)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[2]	122 (39.4) [33.9 - 45.0]
False	93 (30.0)

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
I don't know	95 (30.6)
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.	
13b: It is OK for patients to take TIRF medicines for headache pain.	
True	20 (6.5)
False[2]	232 (74.8) [69.6 - 79.6]
I don't know	58 (18.7)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.	
True[2]	310 (100.0) [98.8 - 100.0]
False	0
I don't know	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.	
True	13 (4.2)
False[2]	267 (86.1) [81.8 - 89.8]
I don't know	30 (9.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine?		
10a: Headache or migraine pain		
Yes	24 (12.4)	8 (6.9)
No[2]	155 (79.9) [73.6 - 85.3]	95 (81.9) [73.7 - 88.4]
I don't know	15 (7.7)	13 (11.2)
10b: Breakthrough pain from cancer		
Yes[2]	140 (72.2) [65.3 - 78.3]	72 (62.1) [52.6 - 70.9]
No	49 (25.3)	31 (26.7)
I don't know	5 (2.6)	13 (11.2)
10c: Dental pain		
Yes	4 (2.1)	4 (3.4)
No[2]	177 (91.2) [86.3 - 94.8]	103 (88.8) [81.6 - 93.9]
I don't know	13 (6.7)	9 (7.8)
10d: Pain after surgery		
Yes	36 (18.6)	29 (25.0)
No[2]	136 (70.1) [63.1 - 76.5]	74 (63.8) [54.4 - 72.5]
I don't know	22 (11.3)	13 (11.2)
10e: Long-lasting pain not from cancer, like arthritis joint pain		
Yes	76 (39.2)	59 (50.9)
No[2]	95 (49.0) [41.7 - 56.2]	41 (35.3) [26.7 - 44.8]
I don't know	23 (11.9)	16 (13.8)
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	81 (41.8) [34.7 - 49.0]	41 (35.3) [26.7 - 44.8]

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
False	56 (28.9)	37 (31.9)
I don't know	57 (29.4)	38 (32.8)
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.		
13b: It is OK for patients to take TIRF medicines for headache pain.		
True	14 (7.2)	6 (5.2)
False[2]	144 (74.2) [67.5 - 80.2]	88 (75.9) [67.0 - 83.3]
I don't know	36 (18.6)	22 (19.0)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.		
True[2]	194 (100.0) [98.1 - 100.0]	116 (100.0) [96.9 - 100.0]
False	0	0
I don't know	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.		
True	7 (3.6)	6 (5.2)
False[2]	170 (87.6) [82.2 - 91.9]	97 (83.6) [75.6 - 89.8]
I don't know	17 (8.8)	13 (11.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Highest Level of Education - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine?				
10a: Headache or migraine pain				
Yes	7 (11.1)	14 (11.4)	8 (7.3)	3 (20.0)
No[2]	49 (77.8) [65.5 - 87.3]	97 (78.9) [70.6 - 85.7]	94 (86.2) [78.3 - 92.1]	10 (66.7) [38.4 - 88.2]
I don't know	7 (11.1)	12 (9.8)	7 (6.4)	2 (13.3)
10b: Breakthrough pain from cancer				
Yes[2]	44 (69.8) [57.0 - 80.8]	76 (61.8) [52.6 - 70.4]	80 (73.4) [64.1 - 81.4]	12 (80.0) [51.9 - 95.7]
No	13 (20.6)	40 (32.5)	25 (22.9)	2 (13.3)
I don't know	6 (9.5)	7 (5.7)	4 (3.7)	1 (6.7)
10c: Dental pain				
Yes	1 (1.6)	5 (4.1)	2 (1.8)	0
No[2]	58 (92.1) [82.4 - 97.4]	106 (86.2) [78.8 - 91.7]	103 (94.5) [88.4 - 98.0]	13 (86.7) [59.5 - 98.3]
I don't know	4 (6.3)	12 (9.8)	4 (3.7)	2 (13.3)
10d: Pain after surgery				
Yes	15 (23.8)	29 (23.6)	19 (17.4)	2 (13.3)

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Highest Level of Education - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
No[2]	39 (61.9) [48.8 - 73.9]	80 (65.0) [55.9 - 73.4]	81 (74.3) [65.1 - 82.2]	10 (66.7) [38.4 - 88.2]
I don't know	9 (14.3)	14 (11.4)	9 (8.3)	3 (20.0)
10e: Long-lasting pain not from cancer, like arthritis joint pain				
Yes	28 (44.4)	56 (45.5)	45 (41.3)	6 (40.0)
No[2]	29 (46.0) [33.4 - 59.1]	48 (39.0) [30.4 - 48.2]	54 (49.5) [39.8 - 59.3]	5 (33.3) [11.8 - 61.6]
I don't know	6 (9.5)	19 (15.4)	10 (9.2)	4 (26.7)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	12 (19.0) [10.2 - 30.9]	48 (39.0) [30.4 - 48.2]	54 (49.5) [39.8 - 59.3]	8 (53.3) [26.6 - 78.7]
False	23 (36.5)	43 (35.0)	24 (22.0)	3 (20.0)
I don't know	28 (44.4)	32 (26.0)	31 (28.4)	4 (26.7)
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.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
True	7 (11.1)	8 (6.5)	2 (1.8)	3 (20.0)
False[2]	43 (68.3) [55.3 - 79.4]	88 (71.5) [62.7 - 79.3]	92 (84.4) [76.2 - 90.6]	9 (60.0) [32.3 - 83.7]

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Highest Level of Education - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
I don't know	13 (20.6)	27 (22.0)	15 (13.8)	3 (20.0)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True[2]	63 (100.0) [94.3 - 100.0]	123 (100.0) [97.0 - 100.0]	109 (100.0) [96.7 - 100.0]	15 (100.0) [78.2 - 100.0]
False	0	0	0	0
I don't know	0	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
True	3 (4.8)	6 (4.9)	2 (1.8)	2 (13.3)
False[2]	52 (82.5) [70.9 - 90.9]	108 (87.8) [80.7 - 93.0]	98 (89.9) [82.7 - 94.9]	9 (60.0) [32.3 - 83.7]
I don't know	8 (12.7)	9 (7.3)	9 (8.3)	4 (26.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Note: "GED or less" includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." "College" includes "Some college/Associate's degree." "BA/BS or MS/MA" includes "Bachelor's degree" and "Master's degree." "Professional or Doctoral degree" includes "Professional or Doctoral degree."

Table 8.1.5: Responses to Questions Linked to Key Risk Message #3 by Age Group of Respondent - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine?				
10a: Headache or migraine pain				
Yes	1 (4.2)	7 (10.8)	17 (13.2)	7 (7.6)
No[2]	20 (83.3) [62.6 - 95.3]	51 (78.5) [66.5 - 87.7]	101 (78.3) [70.2 - 85.1]	78 (84.8) [75.8 - 91.4]
I don't know	3 (12.5)	7 (10.8)	11 (8.5)	7 (7.6)
10b: Breakthrough pain from cancer				
Yes[2]	19 (79.2) [57.8 - 92.9]	43 (66.2) [53.4 - 77.4]	93 (72.1) [63.5 - 79.6]	57 (62.0) [51.2 - 71.9]
No	4 (16.7)	16 (24.6)	31 (24.0)	29 (31.5)
I don't know	1 (4.2)	6 (9.2)	5 (3.9)	6 (6.5)
10c: Dental pain				
Yes	0	2 (3.1)	4 (3.1)	2 (2.2)
No[2]	22 (91.7) [73.0 - 99.0]	57 (87.7) [77.2 - 94.5]	118 (91.5) [85.3 - 95.7]	83 (90.2) [82.2 - 95.4]
I don't know	2 (8.3)	6 (9.2)	7 (5.4)	7 (7.6)
10d: Pain after surgery				
Yes	2 (8.3)	19 (29.2)	30 (23.3)	14 (15.2)
No[2]	20 (83.3) [62.6 - 95.3]	41 (63.1) [50.2 - 74.7]	84 (65.1) [56.2 - 73.3]	65 (70.7) [60.2 - 79.7]

Table 8.1.5: Responses to Questions Linked to Key Risk Message #3 by Age Group of Respondent - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
I don't know	2 (8.3)	5 (7.7)	15 (11.6)	13 (14.1)
10e: Long-lasting pain not from cancer, like arthritis joint pain				
Yes	7 (29.2)	27 (41.5)	53 (41.1)	48 (52.2)
No[2]	15 (62.5) [40.6 - 81.2]	28 (43.1) [30.8 - 56.0]	55 (42.6) [34.0 - 51.6]	38 (41.3) [31.1 - 52.1]
I don't know	2 (8.3)	10 (15.4)	21 (16.3)	6 (6.5)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	17 (70.8) [48.9 - 87.4]	22 (33.8) [22.6 - 46.6]	54 (41.9) [33.2 - 50.9]	29 (31.5) [22.2 - 42.0]
False	4 (16.7)	25 (38.5)	43 (33.3)	21 (22.8)
I don't know	3 (12.5)	18 (27.7)	32 (24.8)	42 (45.7)
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.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
True	0	7 (10.8)	9 (7.0)	4 (4.3)
False[2]	19 (79.2) [57.8 - 92.9]	48 (73.8) [61.5 - 84.0]	98 (76.0) [67.7 - 83.1]	67 (72.8) [62.6 - 81.6]
I don't know	5 (20.8)	10 (15.4)	22 (17.1)	21 (22.8)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				

Table 8.1.5: Responses to Questions Linked to Key Risk Message #3 by Age Group of Respondent - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
True[2]	24 (100.0) [85.8 - 100.0]	65 (100.0) [94.5 - 100.0]	129 (100.0) [97.2 - 100.0]	92 (100.0) [96.1 - 100.0]
False	0	0	0	0
I don't know	0	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
True	0	3 (4.6)	4 (3.1)	6 (6.5)
False[2]	22 (91.7) [73.0 - 99.0]	59 (90.8) [81.0 - 96.5]	113 (87.6) [80.6 - 92.7]	73 (79.3) [69.6 - 87.1]
I don't know	2 (8.3)	3 (4.6)	12 (9.3)	13 (14.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Correct Responses	Patients/Caregivers (N=310) n (%) [95% CI][1]
0 correct responses	0
1 correct response	3 (1.0)
2 correct responses	9 (2.9)
3 correct responses	12 (3.9)
4 correct responses	15 (4.8)
5 correct responses	40 (12.9)
6 correct responses	69 (22.3)
7 correct responses	57 (18.4)
8 correct responses	56 (18.1)
9 correct responses	49 (15.8) [11.9 - 20.4]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Key Risk Message #4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	
True	5 (1.6)
False[2]	295 (95.2) [92.1 - 97.3]
I don't know	10 (3.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.3: Responses to Questions Linked to Key Risk Message #4 by Modality to Complete Survey - Completed Surveys

Key Risk Message #4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.		
True	1 (0.5)	4 (3.4)
False[2]	189 (97.4) [94.1 - 99.2]	106 (91.4) [84.7 - 95.8]
I don't know	4 (2.1)	6 (5.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.4: Responses to Questions Linked to Key Risk Message #4 by Highest Level of Education - Completed Surveys

Key Risk Message #4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
True	4 (6.3)	0	1 (0.9)	0
False[2]	54 (85.7) [74.6 - 93.3]	119 (96.7) [91.9 - 99.1]	107 (98.2) [93.5 - 99.8]	15 (100.0) [78.2 - 100.0]
I don't know	5 (7.9)	4 (3.3)	1 (0.9)	0

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Note: "GED or less" includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." "College" includes "Some college/Associate's degree." "BA/BS or MS/MA" includes "Bachelor's degree" and "Master's degree." "Professional or Doctoral degree" includes "Professional or Doctoral degree."

Table 9.1.5: Responses to Questions Linked to Key Risk Message #4 by Age Group of Respondent - Completed Surveys

Key Risk Message #4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
True	0	1 (1.5)	1 (0.8)	3 (3.3)
False[2]	24 (100.0) [85.8 - 100.0]	62 (95.4) [87.1 - 99.0]	126 (97.7) [93.4 - 99.5]	83 (90.2) [82.2 - 95.4]
I don't know	0	2 (3.1)	2 (1.6)	6 (6.5)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys

Key Risk Message #5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	
True	0
False[2]	308 (99.4) [97.7 - 99.9]
I don't know	2 (0.6)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a: Selling or giving away TIRF medicines is against the law.	
True[2]	306 (98.7) [96.7 - 99.6]
False	2 (0.6)
I don't know	2 (0.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.3: Responses to Questions Linked to Key Risk Message #5 by Modality to Complete Survey - Completed Surveys

Key Risk Message #5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.		
True	0	0
False[2]	192 (99.0) [96.3 - 99.9]	116 (100.0) [96.9 - 100.0]
I don't know	2 (1.0)	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17a: Selling or giving away TIRF medicines is against the law.		
True[2]	192 (99.0) [96.3 - 99.9]	114 (98.3) [93.9 - 99.8]
False	1 (0.5)	1 (0.9)
I don't know	1 (0.5)	1 (0.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.4: Responses to Questions Linked to Key Risk Message #5 by Highest Level of Education - Completed Surveys

Key Risk Message #5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
True	0	0	0	0
False[2]	62 (98.4) [91.5 - 100.0]	122 (99.2) [95.6 - 100.0]	109 (100.0) [96.7 - 100.0]	15 (100.0) [78.2 - 100.0]
I don't know	1 (1.6)	1 (0.8)	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True[2]	62 (98.4) [91.5 - 100.0]	120 (97.6) [93.0 - 99.5]	109 (100.0) [96.7 - 100.0]	15 (100.0) [78.2 - 100.0]
False	0	2 (1.6)	0	0
I don't know	1 (1.6)	1 (0.8)	0	0

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Note: "GED or less" includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." "College" includes "Some college/Associate's degree." "BA/BS or MS/MA" includes "Bachelor's degree" and "Master's degree." "Professional or Doctoral degree" includes "Professional or Doctoral degree."

Table 10.1.5: Responses to Questions Linked to Key Risk Message #5 by Age Group of Respondent - Completed Surveys

Key Risk Message #5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
True	0	0	0	0
False[2]	24 (100.0) [85.8 - 100.0]	64 (98.5) [91.7 - 100.0]	129 (100.0) [97.2 - 100.0]	91 (98.9) [94.1 - 100.0]
I don't know	0	1 (1.5)	0	1 (1.1)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True[2]	24 (100.0) [85.8 - 100.0]	64 (98.5) [91.7 - 100.0]	128 (99.2) [95.8 - 100.0]	90 (97.8) [92.4 - 99.7]
False	0	1 (1.5)	1 (0.8)	0
I don't know	0	0	0	2 (2.2)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys

Key Risk Message #5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.

Correct Responses	Patients/Caregivers (N=310) n (%) [95% CI][1]
0 correct responses	0
1 correct response	6 (1.9)
2 correct responses	304 (98.1) [95.8 - 99.3]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 11.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Question	Patients/Caregivers (N=310) n (%) [95% CI][1]
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.	
13a: TIRF medicines should be stored in a safe place out of the reach of children.	
True[2]	309 (99.7) [98.2 - 100.0]
False	1 (0.3)
I don't know	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	
Wait an hour and see if the person is OK.	6 (1.9)
Get emergency help right away.[2]	273 (88.1) [83.9 - 91.5]
Do nothing.	1 (0.3)
I don't know.	30 (9.7)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.	
True[2]	299 (96.5) [93.7 - 98.2]
False	2 (0.6)
I don't know	9 (2.9)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.	
True[2]	289 (93.2) [89.8 - 95.8]
False	2 (0.6)
I don't know	19 (6.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.1.3: Responses to Questions Linked to Key Risk Message #6 by Modality to Complete Survey - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Question	Modality to Complete Survey	
	Internet (N=194) n (%) [95% CI][1]	Telephone (N=116) n (%) [95% CI][1]
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.		
13a: TIRF medicines should be stored in a safe place out of the reach of children.		
True[2]	193 (99.5) [97.2 - 100.0]	116 (100.0) [96.9 - 100.0]
False	1 (0.5)	0
I don't know	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)		
Wait an hour and see if the person is OK.	6 (3.1)	0
Get emergency help right away.[2]	173 (89.2) [83.9 - 93.2]	100 (86.2) [78.6 - 91.9]
Do nothing.	1 (0.5)	0
I don't know.	14 (7.2)	16 (13.8)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.		
True[2]	188 (96.9) [93.4 - 98.9]	111 (95.7) [90.2 - 98.6]
False	1 (0.5)	1 (0.9)
I don't know	5 (2.6)	4 (3.4)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.		
True[2]	183 (94.3) [90.1 - 97.1]	106 (91.4) [84.7 - 95.8]
False	1 (0.5)	1 (0.9)
I don't know	10 (5.2)	9 (7.8)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.1.4: Responses to Questions Linked to Key Risk Message #6 by Highest Level of Education - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
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.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True[2]	63 (100.0) [94.3 - 100.0]	122 (99.2) [95.6 - 100.0]	109 (100.0) [96.7 - 100.0]	15 (100.0) [78.2 - 100.0]
False	0	1 (0.8)	0	0
I don't know	0	0	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Wait an hour and see if the person is OK.	1 (1.6)	2 (1.6)	3 (2.8)	0
Get emergency help right away.[2]	52 (82.5) [70.9 - 90.9]	109 (88.6) [81.6 - 93.6]	98 (89.9) [82.7 - 94.9]	14 (93.3) [68.1 - 99.8]
Do nothing.	0	1 (0.8)	0	0
I don't know.	10 (15.9)	11 (8.9)	8 (7.3)	1 (6.7)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True[2]	61 (96.8) [89.0 - 99.6]	117 (95.1) [89.7 - 98.2]	107 (98.2) [93.5 - 99.8]	14 (93.3) [68.1 - 99.8]
False	1 (1.6)	0	1 (0.9)	0
I don't know	1 (1.6)	6 (4.9)	1 (0.9)	1 (6.7)

Table 11.1.4: Responses to Questions Linked to Key Risk Message #6 by Highest Level of Education - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Question	Highest Level of Education			
	GED or less (N=63) n (%) [95% CI][1]	College (N=123) n (%) [95% CI][1]	BA/BS or MS/MA (N=109) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True[2]	57 (90.5) [80.4 - 96.4]	114 (92.7) [86.6 - 96.6]	105 (96.3) [90.9 - 99.0]	13 (86.7) [59.5 - 98.3]
False	1 (1.6)	1 (0.8)	0	0
I don't know	5 (7.9)	8 (6.5)	4 (3.7)	2 (13.3)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.
Note: "GED or less" includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." "College" includes "Some college/Associate's degree." "BA/BS or MS/MA" includes "Bachelor's degree" and "Master's degree." "Professional or Doctoral degree" includes "Professional or Doctoral degree."

Table 11.1.5: Responses to Questions Linked to Key Risk Message #6 by Age Group of Respondent - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
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.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True[2]	24 (100.0) [85.8 - 100.0]	64 (98.5) [91.7 - 100.0]	129 (100.0) [97.2 - 100.0]	92 (100.0) [96.1 - 100.0]
False	0	1 (1.5)	0	0
I don't know	0	0	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Wait an hour and see if the person is OK.	0	3 (4.6)	1 (0.8)	2 (2.2)
Get emergency help right away.[2]	24 (100.0) [85.8 - 100.0]	58 (89.2) [79.1 - 95.6]	116 (89.9) [83.4 - 94.5]	75 (81.5) [72.1 - 88.9]
Do nothing.	0	0	1 (0.8)	0
I don't know.	0	4 (6.2)	11 (8.5)	15 (16.3)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True[2]	23 (95.8) [78.9 - 99.9]	63 (96.9) [89.3 - 99.6]	127 (98.4) [94.5 - 99.8]	86 (93.5) [86.3 - 97.6]
False	0	0	1 (0.8)	1 (1.1)
I don't know	1 (4.2)	2 (3.1)	1 (0.8)	5 (5.4)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				

Table 11.1.5: Responses to Questions Linked to Key Risk Message #6 by Age Group of Respondent - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Question	Age Group of Respondent			
	18 - 39 (N=24) n (%) [95% CI][1]	40 - 49 (N=65) n (%) [95% CI][1]	50 - 59 (N=129) n (%) [95% CI][1]	60 or older (N=92) n (%) [95% CI][1]
True[2]	23 (95.8) [78.9 - 99.9]	62 (95.4) [87.1 - 99.0]	121 (93.8) [88.1 - 97.3]	83 (90.2) [82.2 - 95.4]
False	0	1 (1.5)	1 (0.8)	0
I don't know	1 (4.2)	2 (3.1)	7 (5.4)	9 (9.8)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys

Key Risk Message #6: TIRF medicines should be stored in a safe place away from children and properly disposed.

Correct Responses	Patients/Caregivers (N=310) n (%) [95% CI][1]
0 correct responses	0
1 correct response	2 (0.6)
2 correct responses	8 (2.6)
3 correct responses	48 (15.5)
4 correct responses	252 (81.3) [76.5 - 85.5]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Listing 1: Listing of Verbatim Responses to Question #22 (How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?) - Completed Surveys

Verbatim Responses
In each box
Medication is FedExed to me.
One was in each box that contained the spray

Listing 2: Listing of Verbatim Responses to Question #27 (Who offered to explain the Medication Guide to you?) - Completed Surveys

Verbatim Responses
Caregiver
Drug Rep
Lending care representative
PA read it to her
Pharm. Rep.
RELATIVE
Rep from company that makes Subsys
SPOUSE (AN R.N.)
Sale's Rep
Sale's Rep
Someone from the manufacturer
The Dr's PA
drug rep
pharmasuitical representative
someone gave a call

Listing 3: Listing of Verbatim Responses to Question #31 (Questions about the Medication Guide) - Completed Surveys

Verbatim Responses
'On the effect on your teeth. Is it sugar that gives it the taste?' 'I've had a problem with it rotting my teeth.'
Any statement that I was not 100% clear on, I stated to the Doctor or Pharmacist that 'I am not clear about what that means. I take full control of my Healthcare and do not depend on the Doctor completely. I go to another Doctor for a second opinion and I extensively research the combination of medicines that I take. I will not take oral opioids. In fact I told the Doctor I did not want Subsy and the reason why! After my explanation he assured me that the form of delivery is different from the Fentynl Patch, but the long term use on my body is not different. He stated the delivery of the medication is different, and since you refuse to take anything by mouth for pain Subsy might be a good alternative for you. I relented, and agreed to try it beginning with a 15 day supply,100 mcg morning and 100 mcg at night.
DOESNT GIVE ENOUGH INFO ON SERIOUS SIDE EFFECTS MAKES IT SEEM TO HARMLESS SIDE EFFECTS FOR A STRONG NARCOTIC GIVEN WHENALL OTHER PAIN MEDS STOP WORKIMG THIS MAKES SEEM ITS GOING DO GREAT THINGS STOP PAIN OTHER MEDS DONT DOESNT WORK WELL IN MANANGING PAININ FACT DOESNT REALLY WORK ALSO ALOT BAD SIDE EFFECTS BLEED THROUGH RECTUM ALSO VOMIT BLOODWORSE CONSTIPATIONCANT GO AT ALL N MATTER WHAT TRY TAKE ABLE HAVE BOWEL MOVEMENT LIKE STONES INSIDE YOU TO LARGE PASS CUTS RECTUM CANNOT O ON OWN. MIND ALTERING HIGH LOW HAPPY SAD MAD CRazy make others around you scared of your behavior be around you. Cannot get grip reality all this negative no positive outcome from it pain level still 10 plus such great cost make pharmeceutocal company rich ourageous no hospitals or pharmacies afford carry nr insurance COMPANIES WILING PAY. MY INSURANCE COMPANY DIDNT REALIZE OR TOLD OF COST DOCTORS NOT ADVISED WHEN GOING FOR EXCEPTION SO PATIENT ABLE TRY IT CAN GET PAIN MANAGEMENT DOCTORS THROWN OFFAS A PROVIDER AND HARD FIND GET GOOD PAIN MANAGEMENT DOCTORS FDAMADE SO HARD FOR REALLYILL PATIENTS GET PAIN MEDS BECAUSE OF ABUSE BY TEENS/OTHERS TAKING FOR FUN FDA MUST KNOW OF SIDE EFFECTS REALLY BADMAKE PATIENTS SICKER. HARD DETOX VFROM 6 WEEKS STILL Hcing bad bowel problrms worsebeforeta
Doctor instructed me to continue to use SUBSYS in spite of his refusal to refill my Morphine Sulfate, 15 mg., due to the fact that I had THC in my UA. (I'd been out-of-state but still not legal in my state.) I was given TWO conflicting instructions, by SUBSYS and it's distributor: to stop taking it and to continue taking it. Really infuriating.
First I was on the spray now im on the lollis and I thik they are making me have hallucinations and im fixing to tell them to stop giving them me. And the sprays work better than the lolli pops. ive been told there is a patch, but I haven't been offeredit. and its very expensive, theres only one pharmacy in (b) (6) that has it. (b) (6) doesn't have it, and theres only one pharmacy that keeps it its a (b) (6) and no other pharmacys wont order it. and I think that's important you should be able to find your medicine. the spray was mailed to you, but the lollis you cant get in a 100 mile radius its (b) (6) the one (b) (6) will get it but no other (b) (6) will get it and they leave it upon you to find the pharmacy,. you put a lolli pop in your mouth and the thing sticks out it says to knaw on the end- children think theyre suckers cause of the way they look like dumb-dumbs. I think they need to rethink their the way it looks.
Has an addition been added to inform the user that teeth will be damaged and lost with the prolonged use of this product?

Listing 3: Listing of Verbatim Responses to Question #31 (Questions about the Medication Guide) - Completed Surveys

Verbatim Responses
How to dispense (use) the lozenge medication
If I didn't get relief from the first dose,could I take another dose,& how soon after the first dose.
JUST TALKED OVER BASIC QUESTIONS I HAD ABOUT HOW AND WHEN TO USE IT
LIke uh, the dangers of taking the medicine, how often is too much to take it, can I take less of the medicine, can I take more that type of deal. The general safety of taking the negatives and positives of taking the medicine.
No current questions, at the time there were just vocabulary clarifications I needed.
One out of every 3 there is no burning sensation. I feel no instant relief of pain. I cant open the package.
When to begin taking next strength
Why is it only available for cancer patience?
Why is the base of the medicine sugar - bad for teeth serious dental problems why is the medicine based with sugar?
its being strictly guided for cancer patients- its unfair - my insurance doesn't want to pay for it now.

Listing 4: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
Why is the base of the medicine sugar - its bad for your teeth I've had serious dental problems- why is the medicine based with sugar?	Telephone
I take fentanol because I have fibromyalgia and I have arthritis I don't know if it is related or not but my doctors don't even know about it yet. I just found out on Tuesday that I've had a mass in my uterus. I don't know if it is cancer or not.	Telephone
'On the effect on your teeth. Is it sugar that gives it the taste?' 'I've had a problem with it rotting my teeth.' "I've had trouble with Actiq. I don't know if they're genetic or not" "I've had them come off the stick, and I've found that the holder, some are fat and some are skinny." "They break up." "And most important, is the effect on the teeth."	Telephone
I am really sick, I need to call you back, I am really sick. Going outside makes me really sick.	Telephone
I use it for breakthrough pain but not for cancer- I have MS. Well I do have joint pain but that's because of my back pain from surgeries. I am in pain constantly so I don't know how to answer these. I can't see small stuff. It's being strictly guided for cancer patients and its unfair - my insurance doesn't want to pay for it and I have an attorney to fight it- that's wrong.	Telephone
I used subsys for chronic pain until it was too hard to get from the pharmacy.	Telephone
I would like to have my Fentora back - this Fentanyl isn't working.	Telephone
I have severe back pain. I take the Actiq for breakthrough pain for my back. I use this for my back.	Telephone
I use them for breakthough pain from these things - pg 11 (arthritis pain question)	Telephone
And it's hard to stick on sometimes. It really gives you trouble sometimes.	Telephone
First I was on the spray now im on the lollis and I thik they are making me have hallucinations and im fixing to tell them to stop giving them me. And the sprays work better than the lolli pops. ive been told there is a patch, but I haven't been offeredit. and its very expensive, theres only one pharmacy in (b) (6) that has it (b) (6) doesn't have it, and theres only one pharmacy that keeps it its a (b) (6) and no other pharmacys wont order it. and I think that's important you should be able to find your medicine. the spray was mailed to you, but the lollis you cant get in a 100 mile radius its (b) (6) the one (b) (6) will get it but no other (b) (6) will get it and they leave it upon you to find the pharmacy,. you put a lolli pop in your mouth and the thing sticks out it says to knaw on the end- children think theyre suckers cause of the way they look like dumb-dumbs. I think they need to rethink their the way it looks.	Telephone

Listing 4: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
• I took all these pain medications they had me pooping baby arms not to be gross • And waking up somewhere in a ditch • After taking a multitude of narcotics I was taking the patches and people were telling me I was falling asleep in my soup and all kinds of crazy stuff- scary situation • When I was taking the patched I didn't have any realization of the potency of it and the fast acting abilities and the ability to shut down my respiratory system in not taken properly • My experiences 12 years of taking these medications people may have the same problems I had the broken bones, burns, everything else- damaging my liver and kidneys in the process • OxyContin and Morphine and Fentanyl patch they are all potent and very dangerous – When taking them they sent me through a loop the fentanyl patch especially in the 100mg form it would do nothing then 4 hours later I'd become a zombie and not know what I was doing for the next 2 days it was scary stuff	Telephone
The Actiq is slower acting. I had an allergic reaction to Fentora. I itch, breakout and it doesn't help with the pain. It gives me a reaction. I take it for long time pain. Fentora gives me a rash. The second round of fentora I broke out had a rash till bleeding. It hits hard and I have side effects.	Telephone
When you spray it in your mouth, the sprayers don't work properly. I end up being short at the end of the month because I get so many duds. It's not just the one product, it seems to be in every strength. When it does pop, sometimes it doesn't spray. Like there isn't air in it. It seems like there isn't anything to trigger it. It looks fine, but when you go to hit it there's nothing there.	Telephone
One out of every 3 there is no burning sensation. I feel no instant relief of pain. I cant open the package.	Telephone
I have back problems- I don't use it for cancer it's my spine.	Telephone
Right now I'm using the Subsys which is not helping me at all. I have a fractured back from osteoporosis. I fractured my foot, a rib. The one you spray under your tongue, I did not find it as effective. I know I need a stronger dose of it, but my insurance doesn't cover it.	Telephone
"That stuff is highly addictive ok and what they did to me should be criminal, I went through some serious pain and depression and whatever" It was really painful, the withdrawal from fentanyl is one of the worst" I am dependent on opiates I have major pain problems" "they should have provisions to not drop someone cold turkey, believe me it was very painful and uncomfortable"	Telephone
I don't know why I've been coughing all day- my breathing has been yucky- the humidity in [redacted] (b) (6) is awful.	Telephone
"It made me sick as a dog." "There are more dangerous side effects than they tell you on the box." "Still six weeks later and I'm still having bad side effects."	Telephone
Patient passed away, Summer 2015, specific date unknown. "He stopped taking the medication once he was admitted to Hospice in [redacted] (b) (6) and they took him off of it."	Telephone
it gives me dry heaves- I don't take it for recreational purposes.	Telephone
"I didn't take it that long and it made me sick" "I haven't taken it in a couple months"	Telephone

Listing 4: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
I got to get out of bed and put my leg on- Actiq would rot my teeth- He kept me from rolling my wheelchair off the bridge because the pain was so bad- I thought about taking a chainsaw to the rest of my legs the pain was so bad- thats how bad it was. I had surgery on my nose-	Telephone
I have diarrhea and vomit consistently.	Telephone
My other medication was turning me into a zombie. I was taking the patches and all of a sudden boom I'd fall asleep in my soup. I was on that patch for a couple of years and it made me nauseas. I'm good for half of the day then the pain start coming back a little bit, I could function normally prior to that when I'm over doing it, able to obtain normal conversation, my head not bouncing off my shoulders, like a bobble head. You don't know what kind of hell I went through. This medication was a godsend it's just expensive. I had a lot of hoops to get through. I'm shooting it and taking it in my toes. I got one elbow.	Telephone
"As I sit here in pain"	Internet
Only other one I've had when I was diagnosed with my cancer is the like lollipops that were fentanyl that you suck on I didn't like that, they didn't do anything for me having dentures they didn't work so hot" "I've tried all the milligrams of the fentora and the only one that seems works for me is the 400 mg when I take 2 of them every so often" "I got hepatitis C and B through a blood transfusion"	Telephone
DOESNT GIVE ENOUGH INFO ON SERIOUS SIDE EFFECTS MAKES IT SEEM TO HARMLESS SIDE EFFECTS FOR A STRONG NARCOTIC GIVEN WHENALL OTHER PAIN MEDS STOP WORKIMG THIS MAKES SEEM ITS GOING DO GREAT THINGS STOP PAIN OTHER MEDS DONT DOESNT WORK WELL IN MANANGING PAININ FACT DOESNT REALLY WORK ALSO ALOT BAD SIDE EFFECTS BLEED THROUGH RECTUM ALSO VOMIT BLOODWORSE CONSTIPATIONCANT GO AT ALL N MATTER WHAT TRY TAKE ABLE HAVE BOWEL MOVEMENT LIKE STONES INSIDE YOU TO LARGE PASS CUTS RECTUM CANNOT O ON OWN. MIND ALTERING HIGH LOW HAPPY SAD MAD CRazy make others around you scared of your behavior be around you. Cannot get grip reality all this negative no positive outcome from it pain level still 10 plus such great cost make pharmeceutocal company rich ourageous no hospitals or pharmacies afford carry nr insurance COMPANIES WILING PAY. MY INSURANCE COMPANY DIDNT REALIZE OR TOLD OF COST DOCTORS NOT ADVISED WHEN GOING FOR EXCEPTION SO PATIENT ABLE TRY IT CAN GET PAIN MANAGEMENT DOCTORS THROWN OFFAS A PROVIDER AND HARD FIND GET GOOD PAIN MANAGEMENT DOCTORS FDAMADE SO HARD FOR REALLYILL PATIENTS GET PAIN MEDS BECAUSE OF ABUSE BY TEENS/OTHERS TAKING FOR FUN FDA MUST KNOW OF SIDE EFFECTS REALLY BADMAKE PATIENTS SICKER. HARD DETOX VFROM 6 WEEKS STILL Hcing bad bowel problrms worsebeforeta	Internet
Doctor instructed me to continue to use SUBSYS in spite of his refusal to refill my Morphine Sulfate, 15 mg., due to the fact that I had THC in my UA. (I'd been out-of-state but still not legal in my state.) I was given TWO conflicting instructions, by SUBSYS and it's distributor: to stop taking it and to continue taking it. Really infuriating.	Internet

Listing 4: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
Husband passed about two weeks ago	Internet
I'd be doing better if I was feeling better. I just have my pain, the weather has been hot for so many days and my pain acts up.	Internet
When I received a call from you before about doing a survey I had Labyrinthitis. It's like being on the worst amusement park ride ever, shaking and tossing you around back and forth. It's like Hell. It was horrible. I just was so far gone it was terrible.	Telephone
I was on it but it made me hallucinate and sent me to the psych ward. I had really bad hallucinations on it and thought my husband killed himself so I went to the psych ward. It's horrible- it made me hallucinate so bad and I thought my husband was dead- and so I went to the psych ward. It was really bad and now I have to do therapy. I just put our son on the bus and I came into the garage and I saw my husband hanging there, then I heard him in the attic so crawled through the attic and my hands got cut- then I called 911. It made me hallucinate so bad I seen my husband dead.	Telephone

12.7.2 Pharmacy KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number:	Wave 4, 48-month REMS Assessment Version 1.0
Survey Time Period:	31 August 2015 – 16 September 2015
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. (BDSI) Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	15 December 2015

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
BDSI	BioDelivery Sciences International, Inc.
CI	Confidence Interval
CSP	Closed System Pharmacy
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
N/A	Not Applicable
REMS	Risk Evaluation and Mitigation Strategy
SD	Standard Deviation
SCC	Survey Coordinating Center
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

Executive Summary

The 48-month Knowledge, Attitudes, and Behavior (KAB) survey for pharmacists who dispense Transmucosal Immediate Release Fentanyl (TIRF) medicines was conducted as part of the 48-Month TIRF Risk Evaluation and Mitigation Strategy (REMS) Access Program Assessment. The survey launched on 31 August 2015 and closed on 16 September 2015. Food and Drug Administration (FDA) feedback was provided in the 24-month and 36-month Assessment Report Acknowledgement Letters and where applicable these changes were implemented in the 48-month survey. Changes included steps to include a higher percentage of non-supervisory dispensing pharmacists participate in the survey, adding questions addressing CYP3A4 interactions with TIRF medicines and that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid, removing 'Onsolis' as a response option throughout the survey because it is no longer available, and moving specified existing survey questions under key risk messages.

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients. The survey also included questions about whether pharmacists received, read, understood, and used the product-specific educational materials, and included questions about compliance with the REMS requirements.

Invitations (and reminders) were sent to a random sample of pharmacies enrolled in the TIRF REMS Access Program as of 30 June 2015, and were distributed to pharmacists who dispense TIRF products and were known to have received the REMS educational materials. From the total of 607 pharmacists who accessed the survey, 334 (55.0%) pharmacists met eligibility criteria, and of those who met eligibility criteria, 301 (90.1%) completed the survey, exceeding the target of 300 completed surveys.

In general, there is an overall trend across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in pharmacist knowledge and understanding of the key risk messages. Of the 29 components included as part of key risk messages, 20 components of the key risk messages had a response rate >80%, and 7 components had a response rate between 65.1% to 78.7%. Two components within the key risk messages had a correct response rate below the desired threshold of 65% (Component 6c and Component 9e). The correct response rate for Component 6c (*A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 41.9%. This component was added to the 48-month survey based on feedback provided by FDA in the 24-month and the 36-month FDA REMS Acknowledgement Letter. Correct response rate for Component 9e (*Chronic non-cancer pain* is not an indication for which TIRF medicines can be prescribed) was 50.8% for this 48-month survey. Component 9e has had a low correct response rate across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). The survey score for Component 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

The consistently high level of pharmacists' understanding of key risk messages in the latest (48-month) survey indicates that the Education Program for Pharmacists is meeting the goals of the TIRF REMS Access Program. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

1. PHARMACIST SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics indicated for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The FDA has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program was approved by the FDA on 28 December 2011. This report describes the results from the pharmacist surveys conducted for the 48-Month TIRF REMS Access Program Assessment, and reflects the reporting period of 29 October 2014 to 28 October 2015. The 48-month KAB survey launched on 31 August 2015 and closed on 16 September 2015.

The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and their generic equivalents. The TRIG includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. Two companies joined the TRIG during the reporting period: Actavis Laboratories FL, Inc. joined on 6 February 2015 and BDSI replaced Meda Pharmaceuticals on 11 March 2015.

The TIRF REMS Access Program consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. 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 the following:

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.

An important component of the TIRF REMS Access Program Assessment is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS Access Program educational materials, TIRF REMS Access Program Pharmacy Enrollment Form, and Prescribing Information of each product. Administration of the surveys conducted among pharmacies enrolled in the TIRF REMS Access Program is described in the protocol (See Appendix A). Note: Protocol and survey question revisions from the 36-month assessment report are identified as tracked changes.

Data from the surveys, together with other TIRF REMS Access Program evaluation metrics, will be used to determine whether changes need to be made to the TIRF REMS Access Program processes or educational materials to make them more effective in achieving the goals of the TIRF REMS Access Program.

1.1 Changes to the KAB Survey for Pharmacists Based on FDA Feedback

FDA feedback was received on the KAB survey for pharmacists in the 24-month and the 36-month FDA REMS Acknowledgement Letters.

The FDA provided the following feedback to the TRIG on the KAB survey for pharmacists based on results included in the 24-month REMS Assessment Report.

- Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs. Also include a question in the pharmacist survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

- In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

This feedback was provided after the launch of the 36-month KAB survey for pharmacists, thus the changes were incorporated into the 48-month KAB survey for pharmacists and results from the revised survey are included in this 48-month KAB Assessment Report.

The FDA provided the following feedback to the TRIG on the KAB survey for pharmacists based on results included in the 36-month REMS Assessment Report:

- Remove Onsolis as a response option throughout the survey as it is no longer available
- Move existing surveys questions (Question 11a-f) into Key Risk Message 1
- Move an existing surveys question (Question 6a, 6b) into Key Risk Message 2
- Move an existing surveys question (Question 13c-f) into Key Risk Message 4

The 36-month Assessment Report Acknowledgement Letter was received by the TRIG sponsors on 04 August 2015. All requested changes were incorporated into the 48-month KAB survey prior to launch. In an effort to ensure that a higher percentage of non-

supervisory dispensing pharmacists were included for this reporting period, the invitation letter was revised and addressed to "Staff Pharmacist" and disseminated to those pharmacies enrolled in the TIRF REMS Access Program. In previous waves, the invitation letter was addressed to the Pharmacist-in-Charge. In order to incorporate FDA's feedback in the 48-month Pharmacist KAB survey, the survey launch date originally scheduled for the second week of August was delayed until 31 August 2015.

2. PHARMACIST SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are 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.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey also collects data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions developed to test pharmacist understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Sample

A sample of 300 pharmacists who dispense TIRF products and were known to have received the REMS educational materials was planned for this fourth KAB survey which was expected to be open from 31 August 2015 to 20 October 2015. The survey sample size was determined based on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Subjects were recruited from a random sample of pharmacies enrolled in the TIRF REMS Access Program as of 30 June 2015. All pharmacists who worked at the enrolled pharmacy were eligible to participate, which could result in multiple completed surveys per pharmacy. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation (UBC), or the FDA were not eligible to participate nor were respondents who participated in the previous waves of the survey (the 12-month TIRF REMS Access Program Assessment, the 24-month TIRF REMS Access Program Assessment, or the 36-month TIRF REMS Access Program Assessment).

3.1.2 Recruitment

Subjects were recruited via an invitation letter sent through the United States Postal Service (USPS) or via fax (see Section 5.1.1 for more detail).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; thus additional mailings were distributed to non-respondents from the original sample to maximize participation.

Each letter of invitation included a unique code needed to access the survey.
Three categories of pharmacies were sampled: Closed System Pharmacy (CSP), Inpatient Pharmacy, and Outpatient Pharmacy. Each pharmacy was provided a unique access code based on their pharmacy type because some questions in the survey were specific to only one type of pharmacy. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed).

Pharmacists were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. The survey was estimated to take approximately 15-20 minutes to complete.

All respondents who completed the survey and provided their contact information were mailed a $50 gift card for participating. The mailing also included a copy of the Important Safety Information (ISI) and a copy of the correct answers to the key risk message questions.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the pharmacists' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by

providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the survey protocol (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines in opioid non-tolerant patients and under what conditions a patient is considered opioid tolerant.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	***True***
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	***False***
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	***False***
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used in opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***
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:	
11a	8 mg oral hydromorphone/day	***True***
11b	60 mg oral morphine/day	***True***
11c	30 mg oral oxycodone/day	***True***
11d	25 mcg transdermal fentanyl/hour	***True***
11e	25 mg oral oxymorphone/day	***True***
11f	An equianalgesic dose of another oral opioid	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the pharmacist's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients, and the timing of administration of the TIRF medicine in relation to the around-the-clock opioid therapy to ensure the patient is considered opioid tolerant.

Key Risk Message 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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
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***
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.	***False***
6c	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	***True***
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	Chronic non-cancer pain	***No***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the pharmacist's knowledge of the risk factors for opioid abuse and importance in monitoring for signs of abuse in patients who take TIRF medicines.

Key Risk Message 3: **TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.**		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement about TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the pharmacist's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***
13	Please answer True, False, or I don't know for each statement about TIRF medicines.	
13c	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	***False***

3.3 Additional Questions

The survey also contained questions (Question 12a-f) about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors. The following questions about behaviors were asked after the key risk message questions:

Question No.	Question
12	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
12a	Ask patients (or their caregivers) about the presence of children in the home
12b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
12c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
12d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
12e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
12f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible pharmacists who completed the survey. Eligible pharmacists were defined as those respondents who answered Yes to Question 1 (agree to take part in survey), and Yes to Question 3 (work at a pharmacy that is enrolled in the TIRF REMs Access Program), and No to Question 2 (participated in past survey) and No to Question 4 (worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA). A survey was considered "completed" when an eligible pharmacist answered all relevant questions.

4.2 Primary Analyses

Primary analyses were performed for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/component included in the key risk message. Confidence intervals (95% CI) were calculated using the exact binomial method around the percentage of correct responses.

Primary analyses were then stratified by questions/characteristics of interest:

1) Those who indicated they both received and read the Medication Guide and Full Prescribing Information versus those who did not and those who responded they did not or did not know whether they had (Questions 18-21).
2) Whether the survey was completed via the internet or telephone
3) Time in pharmacy practice (Question 28).
4) The number of times per month they dispensed TIRF medicines within the last 6 months (Question 25).

Stratified analyses were conducted only when at least two of the stratified response categories had at least 50 respondents (e.g., for analysis 2 above, at least 50 pharmacists had to respond they completed the survey via the internet and at least 50 had to respond they completed it by telephone in order for that analysis to be conducted).

4.3 Secondary Analyses

As an indicator of the overall level of comprehension of the entire key risk message, descriptive analyses of the number and percentage of responders who answered various proportions of the key risk message components correctly are presented (e.g., the proportion who answered one question in the key risk message correctly, those who answered two questions correctly, those who answered three component questions correctly, etc.). Confidence intervals (95% CI) were calculated for the proportion of respondents who answered all component questions of the key risk message correctly.

4.4 Pharmacist Report of a Potential Adverse Event, Product Complaint, or Medical Information Request during the Survey

A pharmacist may have reported a potential adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the event or complaint, the verbatim response, and the pharmacist's contact information, if provided. The pharmacist was also informed that a representative from the appropriate TIRF medicine sponsor may contact him/her to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the pharmacist's responses to questions in the KAB survey are summarized in this section; stratified analysis tables and overall listings are provided in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

In an effort to ensure that a higher percentage of non-supervisory dispensing pharmacists were included for this reporting period, the invitation letter was revised and addressed to "Staff Pharmacist" and disseminated to those pharmacies enrolled in the TIRF REMS Access Program (question added as requested by the FDA). A total of 4906 pharmacists were identified and all were sent letters inviting them to participate in this survey (Table 1). Of those invited to participate, 571 were inpatient pharmacists, 2478 were outpatient pharmacists, and 36 were pharmacists practicing in CSPs (no CSP outpatient pharmacists participated in the survey; see Section 5.2.7). An additional 4593 reminder letters were sent to non-responders (See Section 3.1 for survey methodology details). Most pharmacists received more than 1 reminder letter. The survey was closed once the target number of 300 completed surveys was achieved.

As noted in Section 3.1 availability of the survey was expected to extend through 20 October 2015. The survey launch date had been delayed in order to incorporate FDA feedback on the survey received in the 36-Month FDA Assessment Report Acknowledgement Letter. Successful recruitment resulted in the survey closing earlier than expected on 16 September 2015.

From the total of 607 pharmacists who accessed the survey, 334 (55.0%) pharmacists met eligibility criteria, and of those who met eligibility criteria, 301 (90.1%) completed the survey. Of these 301 pharmacists, 293 (97.3%) completed the survey online, and 8 (2.7 %) completed it by telephone (Table 3).

Table 1. Survey Participant Administration Results

Summary Statistic	N	%
Number of invitations distributed	4906	
Number of invitations returned as undeliverable	45	
Number of reminder letters distributed	4593	
All Respondents [1]	607	12.5
Eligible Respondents [2]	334	55.0
Completed survey [3]	301	90.1
Did not complete the survey [3]	33	9.9
Respondents not eligible [2,4]	273	45.0

[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentages are based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

As shown in Table 2, of the 607 pharmacists who accessed the survey, a total of 426 pharmacists (70.2%) agreed to participate in this survey. During the screening process it was determined 92 respondents were not eligible to participate in the survey because they either did not agree to participate in the survey (1 respondent), indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before (61 respondents), worked in pharmacies that were not enrolled or they did not know whether their pharmacy was enrolled in the TIRF REMS Access Program (27 respondents), or indicated they, or an immediate family member, had worked for a TRIG company, UBC, or FDA in the past or the respondent did not know if they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past (2 respondents). Thus, there were 334 eligible participants; with 301 (90.1%) of these pharmacists completing the survey (Table 2).

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists (N=607) n (%)	
	n	%
Question 1: Do you agree to participate in this survey?		
Yes	426	70.2
No [1]	1	0.2
Discontinued	180	29.7
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.		
Yes [1]	9	1.5
No	365	60.1
I don't know [1]	52	8.6
Question not asked [2]	1	0.2
Discontinued	180	29.7

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists (N=607) n (%)	
	n	%
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?		
Yes	338	55.7
No[1]	9	1.5
I don't know [1]	18	3.0
Question not asked [2]	62	10.2
Discontinued	180	29.7
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply. [3]		
Actavis Laboratories FL, Inc. [1]	1	0.2
Anesta, LLC[1]	0	
BioDelivery Services International, Inc. (BDSI) [1]	0	
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) [1]	0	
Depomed, Inc. [1]	0	
Galena Biopharma, Inc [1]	0	
Insys Therapeutics, Inc. [1]	0	
Mallinckrodt Pharmaceuticals [1]	2	0.3
McKesson Specialty Care Solutions [1]	0	
Mylan, Inc.[1]	1	0.2
Par Pharmaceutical, Inc. [1]	2	0.3
RelayHealth [1]	0	
Teva Pharmaceuticals, Ltd. [1]	1	0.2
United BioSource Corporation [1]	0	
FDA [1]	0	
None of these apply [4]	334	55.0
I don't know [1]	2	0.3

Table 2. Survey Participant Screening Results

Question	Screened Pharmacists (N=607) n (%)	
	n	%
Prefer not to answer [1]	0	
Question not asked [2]	89	14.7
Discontinued	180	29.7

[1] Ineligible to participate in the survey.

[2] Question not asked due to previous termination response.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Ineligible to participate in the survey if selected additionally to another response.

Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

Pharmacists taking the survey online took a mean of 15 minutes to complete it, while those taking it by telephone took a mean of 17 minutes (Table 3).

Table 3. Time to Complete Survey for Completers Only

Time to Complete Survey for Completers (Minutes)			
Summary Statistic	Telephone	Internet	Total [1]
N	8	293	301
Mean (± SD)	17.53 (2.755)	15.19 (8.913)	15.25 (8.812)
Minimum	15.3	4.7	4.7
Median	16.27	12.78	12.93
Maximum	21.5	68.4	68.4
Category			
0 – <5 Minutes	0	1	1
5 – <10 Minutes	0	97	97
10 – <15 Minutes	0	77	77
15 – <20 Minutes	6	58	64

Table 3. Time to Complete Survey for Completers Only

Time to Complete Survey for Completers (Minutes)			
20 – <25 Minutes	2	34	36
25 – <30 Minutes	0	9	9
30 Minutes or More	0	17	17

[1] Number of eligible pharmacists completing the survey (See Table 1).
SD = Standard Deviation

5.1.2 Description of Eligible Pharmacists who Completed the Survey

The characteristics of pharmacists who completed the survey are shown in Table 4.

Most pharmacists (245; 81.4%) functioned as the pharmacist-in-charge for the TIRF REMS Access Program where they work. Despite efforts to ensure that a higher percentage of non-supervisory dispensing pharmacists were included for this reporting period, only 17.6% of respondents indicated they were not the pharmacist-in-charge.

The majority of pharmacists had dispensed a TIRF medicine either not at all (118; 39.2%) or 1 to 2 times per month (112; 37.2%) within the past 6 months. The most frequently dispensed TIRF medicine within the 6 months prior to taking the survey was Actiq® or generic Actiq® (117; 63.9%).

The majority of pharmacists who completed the survey were male (192; 63.8%), and out of the 301 eligible pharmacists, 195 (64.8%) had been a practicing pharmacist for 11 or more years. Most participants (119; 39.5%) were from the South, followed by the Northeast (71; 23.6%), Midwest (61; 20.3%) and West (47; 15.6%), regions of the United States (US). There was 1 respondent from Puerto Rico identified as “Other” in Table 4 below.

Table 4. Description of Eligible Pharmacists

Question	Eligible/Completed Pharmacists N=301[1]	
	n	%
Question 24: Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?		
Yes	245	81.4
No	53	17.6
I don't know	3	1.0
Question 25: On average, how many times per month have you dispensed TIRF medicines within the last 6 months		
None	118	39.2
1-2 times per month	112	37.2
3-5 times per month	25	8.3
More than 5 times per month	29	9.6
I don't remember	17	5.6
Question 26: Please select the TIRF medicine(s) that you have dispensed within the last 6 months (select all that apply): [2,3]		
Abstral®	12	6.6
Actiq® or generic Actiq®	117	63.9
Fentora®	63	34.4
Lazanda®	13	7.1
Subsys®	58	31.7
N/A (answered None to Question 25)	118	
Question 27: What is your gender?		
Male	192	63.8
Female	101	33.6
Prefer not to answer	8	2.7
Question 28: In total, how many years have you been a practicing pharmacist?		
Less than 3 years	17	5.6
3-5 years	33	11.0
6-10 years	51	16.9
11-15 years	36	12.0
More than 15 years	159	52.8
Prefer not to answer	5	1.7

Table 4. Description of Eligible Pharmacists

Question	Eligible/Completed Pharmacists N=301[1]	
	n	%
Geographic Distribution (based on Question 29 - In which state do you practice?)? [4]		
Northeast	71	23.6
Midwest	61	20.3
South	119	39.5
West	47	15.6
Other	1	0.3
Prefer not to answer	2	0.7

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Percentages are calculated based on the number of respondents to whom the question was presented.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

5.1.3 TIRF Medicines Educational Materials

Pharmacists were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide (Table 5). Almost all pharmacists reported they had received or had access to the Full Prescribing Information and the Medication Guide (299; 99.3%; and 300; 99.7%, respectively). Of those with access to these materials, 82.6% and 87.7%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide.

Table 5. Responses to Questions About TIRF Medicines Educational Materials

Question	Eligible/Completed Pharmacists N=301[1]	
	n	%
Question 18: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?		
Yes	299	99.3
No	0	
I don't know	2	0.7

Table 5. Responses to Questions About TIRF Medicines Educational Materials

Question	Eligible/Completed Pharmacists N=301[1]	
	n	%
Question 19: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense? [2]		
Yes	247	82.6
No	45	15.1
I don't know	7	2.3
N/A (answered No or I don't know to Question 18)	2	
Question 20: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?		
Yes	300	99.7
No	0	
I don't know	1	0.3
Question 21: Did you read the Medication Guide for the TIRF medicine(s) that you dispense? [2]		
Yes	263	87.7
No	30	10.0
I don't know	7	2.3
N/A (answered No or I don't know to Question 20)	1	
Question 22: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes [3]	5	1.7
No	283	94.0
I don't know	13	4.3

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

[3] Verbatim text for questions about the information in the Full Prescribing Information or the Medication Guide is presented in Appendix B, Listing 1.

5.2 Key Risk Messages

5.2.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines in opioid non-tolerant patients and under what conditions a patient is considered opioid tolerant.

A high percentage of pharmacists knew that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer (92.7%, 95% CI: 89.1-95.4) and are those who are currently taking opioid therapy (87.4%, 95% CI: 83.1-90.9) (Table 6). In addition, most understood that cancer patients with no known contraindications to the drug fentanyl, but who are not taking around-the-clock opioid therapy, are not considered opioid tolerant (82.4%, 95% CI: 77.6-86.5).

Ninety-one percent (91.0%, 95% CI: 87.2-94.0) of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (95.3%, 95%CI: 92.3-97.4). Eighty-five percent (85.4%, 95% CI: 80.9-89.2) were aware that TIRF medicines may not be used to treat opioid non-tolerant patients (85.4%). Similarly, 80.7% (95% CI: 75.8-85.0) of pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product.

The majority of pharmacists were aware of the regimens that defined an opioid-tolerant patient: 8 mg oral hydromorphone/day (78.8%, 95% CI: 73.7-83.2), 60 mg oral morphine/day (89.7%, 95% CI: 85.7-92.9), 30 mg oral oxycodone/day (77.1%, 95%CI: 71.9-81.7), 25 mcg transdermal fentanyl/hour (77.1%; 95% CI: 71.9-81.7), 25 mg oral oxymorphone/day (73.4%, 95% CI: 68.1-78.3), and an equianalgesic dose of another oral opioid (65.1%, 95% CI: 59.4-70.5).

Overall, 29.6% (95% CI: 24.5-35.1) of respondents answered all 13 components of key risk message 1 correctly, 51.5% missed no more than one component and 63.8% missed no more than two.

Analyses stratified by whether the Full Prescribing Information and Medication Guide were received and read (Received and read: N=273; Did not receive or read: N=28) and by modality for completing the survey (internet [N=293] versus telephone [N=8]) were not performed for any of the key risk messages because they did not meet the criteria of ≥50 respondents within at least two response categories.

Stratification by time in practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any evident trends (Appendix B).

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer		
True [3]	279	92.7 (89.1 - 95.4)
False	22	7.3
I don't know	0	
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	27	9.0
False [3]	263	87.4 (83.1 - 90.9)
I don't know	11	3.7
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	44	14.6
False [3]	248	82.4 (77.6 - 86.5)
I don't know	9	3.0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [3]	274	91.0 (87.2 - 94.0)
False	19	6.3
I don't know	8	2.7

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [3]	287	95.3 (92.3 - 97.4)
False	4	1.3
I don't know	10	3.3
7c: TIRF medicines may be used in opioid non-tolerant patients.		
True	35	11.6
False [3]	257	85.4 (80.9 - 89.2)
I don't know	9	3.0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True [3]	243	80.7 (75.8 - 85.0)
False	45	15.0
I don't know	13	4.3
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:		
11a: 8 mg oral hydromorphone/day		
True [3]	237	78.7 (73.7 - 83.2)
False	30	10.0
I don't know	34	11.3
11b: 60 mg oral morphine/day.		
True [3]	270	89.7 (85.7 - 92.9)

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
False	11	3.7
I don't know	20	6.6
11c: 30 mg oral oxycodone/day		
True [3]	232	77.1 (71.9 - 81.7)
False	41	13.6
I don't know	28	9.3
11d: 25 mcg transdermal fentanyl/hour		
True [3]	232	77.1 (71.9 - 81.7)
False	42	14.0
I don't know	27	9.0
11e: 25 mg oral oxymorphone/day		
True [3]	221	73.4 (68.1 - 78.3)
False	36	12.0
I don't know	44	14.6
11f: An equianalgesic dose of another oral opioid		
True [3]	196	65.1 (59.4 - 70.5)
False	49	16.3
I don't know	56	18.6
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	1	0.3
2 correct responses	1	0.3
3 correct responses	2	0.7
4 correct responses	4	1.3

Table 6. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
5 correct responses	5	1.7
6 correct responses	9	3.0
7 correct responses	13	4.3
8 correct responses	11	3.7
9 correct responses	30	10.0
10 correct responses	33	11.0
11 correct responses	37	12.3
12 correct responses	66	21.9
13 correct responses	89	29.6 (24.5 - 35.1)

[1] Number of eligible pharmacists completing the survey (See Table 1).

[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

[3] Indicates the correct response(s) to each question or component within a question.

5.2.2 Key Risk Message 2

Key Risk Message 2 refers to the pharmacist's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients, and the timing of administration of the TIRF medicine in relation to the around-the-clock opioid therapy to ensure the patient is considered opioid tolerant.

Sixty-nine percent (69.1%, 95% CI: 63.5-74.3) of pharmacists correctly indicated that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time, and 82.1% (95% CI: 77.2-86.2) correctly indicated that a cancer patient who had been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain (Table 7). Forty-two percent (41.9%; 95% CI: 36.2-47.7) understood that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (question added as requested by the FDA).

In addition, 92.0% of pharmacists (95% CI: 88.4-94.8) were aware that TIRF medicines are indicated for opioid-tolerant patients with breakthrough pain from cancer and not for patients with acute or postoperative pain (90.0%, 95% CI: 86.1-93.2), headache or migraine pain (93.0%, 95% CI: 89.5-95.6), or dental pain (98.3%, 95% CI: 96.2-99.5). Fifty-one percent (50.8%, 95% CI: 45.0 - 56.6) correctly responded that TIRF medicines should not be prescribed for chronic non-cancer pain.

Overall, 22.3% (95% CI: 17.7-27.4) correctly answered all components of the key risk message; 45.6% missed no more than one component question, and 70.2% missed no more than two of the eight components.

Stratification by time in practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any evident trends (Appendix B).

Table 7. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	70	23.3
False [3]	208	69.1 (63.5 - 74.3)
I don't know	23	7.6
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.		
True	37	12.3
False [3]	247	82.1 (77.2 - 86.2)
I don't know	17	5.6
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True [3]	126	41.9 (36.2 - 47.7)
False	136	45.2
I don't know	39	13.0

Table 7. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	22	7.3
No [3]	271	90.0 (86.1 - 93.2
I don't know	8	2.7
9b: Headache or migraine pain		
Yes	12	4.0
No [3]	280	93.0 (89.5 - 95.6)
I don't know	9	3.0
9c: Dental pain		
Yes	2	0.7
No [3]	296	98.3 (96.2 - 99.5)
I don't know	3	1.0
9d: Breakthrough pain from cancer		
Yes [3]	277	92.0 (88.4 - 94.8)
No	24	8.0
I don't know	0	

Table 7. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
9e: Chronic non-cancer pain		
Yes	131	43.5
No [3]	153	50.8 (45.0 - 56.6)
I don't know	17	5.6
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	2	0.7
2 correct responses	2	0.7
3 correct responses	11	3.7
4 correct responses	26	8.6
5 correct responses	49	16.3
6 correct responses	74	24.6
7 correct responses	70	23.3
8 correct responses	67	22.3 (17.7 - 27.4)

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] All confidence intervals are exact binomial 95% confidence intervals.
[3] Indicates the correct response(s) to each question or component within a question.

5.2.3 Key Risk Message 3

Key Risk Message 3 refers to the pharmacist's knowledge of the risk factors for opioid abuse and importance in monitoring for signs of abuse in patients who take TIRF medicines.

Results in Table 8 show that 97.3% (95% CI: 94.8-98.8) of pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines. In addition, most respondents correctly indicated that a personal history of psychiatric illness is a risk factor for opioid abuse (75.4%, 95% CI: 70.1-80.2), that a personal history of past or

current alcohol or drug abuse or family history of drug or alcohol abuse is a risk factor for opioid abuse (98.7%, 95% CI: 96.6-99.6), and that TIRF medicines can be abused in a manner similar to other opioid agonists (95.7%, 95% CI: 92.7-97.7).

Overall, 69.1% (95% CI: 63.5-74.3) of pharmacists correctly answered all components of the key risk message, and 98% missed no more than one of the 4 component questions.

Stratification by time in practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any evident trends (Appendix B).

Table 8. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics

Question	Eligible/Completed Pharmacists N=301 [1]	
	N	% (95% CI) [2]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [3]	293	97.3 (94.8 - 98.8)
False	7	2.3
I don't know	1	0.3
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes [3]	227	75.4 (70.1 - 80.2)
No	43	14.3
I don't know	31	10.3
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [3]	297	98.7 (96.6 - 99.6)
No	2	0.7
I don't know	2	0.7

Table 8. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics

Question	Eligible/Completed Pharmacists N=301 [1]	
	N	% (95% CI) [2]
Question 10: Please answer True, False, or I don't know for each statement about TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True [3]	288	95.7 (92.7 - 97.7)
False	8	2.7
I don't know	5	1.7
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	0	
2 correct responses	6	2.0
3 correct responses	87	28.9
4 correct responses	208	69.1 (63.5 - 74.3)

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] All confidence intervals are exact binomial 95% confidence intervals.
[3] Indicates the correct response(s) to each question or component within a question.

5.2.4 Key Risk Message 4

Key Risk Message 4 refers to the pharmacist's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Almost all pharmacists (93.4%; 95% CI: 89.9-95.9) understood TIRF medicines are not interchangeable with each other regardless of the route of administration; 92.7% (95% CI: 89.1-95.4) understood the conversion of one TIRF medicine to another may result in a fatal overdose; and 92.7% (95% CI: 89.1-95.4) understood that dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (Table 9). Almost all pharmacists (98.3%, 95% CI: 96.2-99.5) correctly indicated that TIRF medicines with the same route of administration cannot be substituted with each other if the pharmacy is out of stock.

Overall, 80.7% (95% CI: 75.8-85.0) of pharmacists correctly answered all components of the key risk message, 97% missed no more than one of the 4 component questions.

Stratification by time in practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any evident trends (Appendix B).

Table 9. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	14	4.7
False [3]	281	93.4 (89.9 - 95.9)
I don't know	6	2.0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True [3]	279	92.7 (89.1 - 95.4)
False	11	3.7
I don't know	11	3.7
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True [3]	279	92.7 (89.1 - 95.4)
False	14	4.7
I don't know	8	2.7

Table 9. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	% (95% CI) [2]
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.		
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.		
True	3	1.0
False [2]	296	98.3% (96.2 - 99.5)
I don't know	2	0.7
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	2	0.7
2 correct responses	7	2.3
3 correct responses	49	16.3
4 correct responses	243	80.7 (75.8 - 85.0)

[1] Number of eligible pharmacists completing the survey (See Table 1).
[2] All confidence intervals are exact binomial 95% confidence intervals.
[3] Indicates the correct response(s) to each question or component within a question.

5.2.5 Other Survey Questions

5.2.5.1. Additional Questions about TIRF Medicines Safety

Table 10 summarizes the pharmacists' responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. Most pharmacists (91.4%) correctly indicated that use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient as potentially fatal respiratory depression could occur(question added as requested by the FDA) .

The majority of pharmacists correctly indicated that a family history of asthma is not a risk factor for opioid abuse (82.7%).

In addition, 92.7% of pharmacists correctly indicated that TIRF medicines may not be sold, loaned, or transferred to another pharmacy, and that pharmacy staff who dispense TIRF

medicines must be educated on the requirements of the TIRF REMS Access Program (90.7%). Thirteen (86.7%) inpatient pharmacists correctly indicated that it is not OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for home use (Table 11).

Table 10. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	%
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6d: Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.		
True [2]	275	91.4
False	8	2.7
I don't know	18	6.0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8c: A family history of asthma		
Yes	33	11.0
No[2]	249	82.7
I don't know	19	6.3
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.		
13a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.		
True	7	2.3
False [2]	279	92.7
I don't know	15	5.0
13b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.		
True[2]	273	90.7

Table 10. Responses to Additional Questions about the Safe Use of TIRF Medicines

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	%
False	23	7.6
I don't know	5	1.7

[1] Number of eligible pharmacists who completed the survey (See Table 1).
[2]Indicates the correct response(s) to each question or component within a question.

Table 11. Responses to Additional Questions about the Safe Use of TIRF Medicines: Question Asked of Inpatient Pharmacists

Question	Eligible/Completed Pharmacists N=15 [1]	
	n	%
Question 17: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient pharmacists, only)		
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.[2]		
True	0	
False [3]	13	86.7
I don't know	2	13.3

[1] Number of eligible inpatient pharmacists who completed the survey
[2] This question is presented only to the sub-group of inpatient pharmacists. Percentages are based on this subgroup of N=15.
[3] Indicates the correct response(s) to each question or component within a question.

5.2.5.2 Pharmacist Activities When Dispensing TIRF Medicines

Pharmacists were asked about specific activities performed when dispensing TIRF medicines (Table 12).

Of the 301 eligible pharmacists who completed the survey, 59.8% responded they always ask their patients (or a patient's caregiver) about the presence of children in the home; 22.3% responded that they ask only with the first prescription. Additionally, 78.1% responded they always instruct patients (or their caregivers) not to share TIRF medicines; 71.8% responded they always counsel patients (or their caregivers) that accidental exposure to TIRF medicines

by a child may be fatal, 79.1% responded they always instruct patients (or their caregivers) to keep TIRF medicines out of reach of children, 69.4% responded they always instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines, and 92.4% responded they always give patients (or their caregivers) the Medication Guide for TIRF medicine.

Table 12. Responses to Questions about Activities When Dispensing TIRF Medicines

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	%
Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.		
12a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	180	59.8
Only with the first prescription	67	22.3
Sometimes	36	12.0
Never	9	3.0
I don't know	9	3.0
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	235	78.1
Only with the first prescription	42	14.0
Sometimes	14	4.7
Never	6	2.0
I don't know	4	1.3
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	216	71.8
Only with the first prescription	48	15.9
Sometimes	27	9.0
Never	4	1.3
I don't know	6	2.0

Table 12. Responses to Questions about Activities When Dispensing TIRF Medicines

Question	Eligible/Completed Pharmacists N=301 [1]	
	n	%
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	238	79.1
Only with the first prescription	39	13.0
Sometimes	16	5.3
Never	4	1.3
I don't know	4	1.3
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	209	69.4
Only with the first prescription	66	21.9
Sometimes	20	6.6
Never	3	1.0
I don't know	3	1.0
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	278	92.4
Only with the first prescription	14	4.7
Sometimes	4	1.3
Never	2	0.7
I don't know	3	1.0

[1] Number of eligible pharmacists completing the survey (See Table 1).

Specific pharmacy types (inpatient, outpatient, and CSP pharmacies) were each asked a single, different question regarding pharmacy systems and processes. Question 14 was presented only to respondents from inpatient pharmacies (N=15) as identified through the access code entered by the respondent (Table 13). Of the 15 respondents, 53.3% reported their pharmacy has processes to ensure compliance with the TIRF REMS Access Program requirements.

Table 13. Responses to All Questions about Activities When Dispensing TIRF Medicines: Asked of Inpatient Pharmacies Only

Question	Eligible/Completed Inpatient Pharmacists N=15 [1]	
	n	%
Question 14: Does the inpatient pharmacy where you work have an established 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? [Inpatient pharmacists only] [2]		
Yes	8	53.3
No	7	46.7
I don't know	0	

[1] Number of eligible inpatient pharmacists who completed the survey.

[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of inpatient pharmacists to whom this question was presented.

Question 15 was presented only to pharmacy respondents from outpatient pharmacies (n=286) as identified through the access code entered by the respondent. This sub-population did not include respondents from CSPs (Table 14). Of the 286 respondents, 91.6% reported their pharmacy processes prescriptions for TIRF medicines through their pharmacy management system.

Table 14. Responses to All Questions about Activities When Dispensing TIRF Medicines: Outpatient Pharmacists Only

Question	Eligible/Completed Outpatient Pharmacists N=286 [1]	
	n	%
Question 15: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? [Outpatient pharmacists only] [2]		
Yes	262	91.6
No	10	3.5
I don't know	14	4.9

[1] Number of eligible outpatient pharmacists who completed the survey.

[2] This question is presented only to a sub-group of pharmacists. Percentages are based on the number of outpatient pharmacists to whom this question was presented.

Question 16 (*Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?***)** was presented only to pharmacy respondents from CSPs; however, no CSP outpatient pharmacists participated in the survey.

5.3 Spontaneous Reporting of Potential Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N=301, Table 1), there were 3 reports of a potential adverse event or product complaint associated with the use of TIRF medicines made within the survey free text field during the online survey. Verbatim statements are provided in Appendix B, Listing 2.

6. DISCUSSION AND CONCLUSIONS

Discussion

Survey invitations (and reminders) were sent to a random sample of pharmacies enrolled in the TIRF REMS Access Program. From among those who responded to the invitation, 301 pharmacists completed the survey. Thus, the required sample size was achieved within the planned survey period.

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients. The survey also included questions about the pharmacists' access to educational materials for TIRF medicines.

Despite efforts to ensure that a higher percentage of non-supervisory dispensing pharmacists were included for this reporting period, only 17.6% of respondents indicated they were not the pharmacist-in-charge (question added as requested by FDA).

Of the 29 components included as part of key risk messages, 20 components of the key risk messages had a response rate >80%, and 7 components had a response rate between 65.1% to 78.7%. Two components within the key risk messaged had a correct response rate below the desired threshold of 65% (Component 6c and Component 9e).

The correct response rate for Component 6c (*A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 41.9%. This component was added to the 48-month survey based on feedback provided by FDA in the 24-month and the 36-month FDA REMS Acknowledgement Letter (See Section 1.1).

Correct response rate for Component 9e (*Chronic non-cancer pain* is not an indication for which TIRF medicines can be prescribed) was 50.8% for this 48-month survey, which fell below the desired level of understanding of 65%. Component 9e has had a low correct response rate across all pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). However, the correct response rate is trending up (Table 15). The

survey score for Component 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

As shown in Table 15, there is a clear and consistent indication of improvement (i.e., numeric trend) in knowledge and understanding of the key risk messages. Table 15 includes key risk messages and questions/components within each key risk message as presented in the 48-month survey. It is important to note the question/component numbering, wording, and association with a specific key risk message may have changed across survey waves based on FDA feedback or other decisions made by the TRIG.

Table 15. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients					
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: [1]				
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (*Correct Response True*) [1]	12.6[2]	90.3 (86.4, 93.4)	93.7 (90.3, 96.1)	92.7 (89.1 - 95.4)
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response "False"*)	80.1[2]	80.7 (75.7, 85.0)	87.0 (82.7, 90.6)	87.4 (83.1 - 90.9)
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response False*) [1]	15.6[2]	76.0 (70.8, 80.7)	78.7 (73.6, 83.2)	82.4 (77.6 - 86.5)
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response True*)	86.1 (81.7, 89.8)	86.0 (81.6, 89.7)	90.7 (86.8, 93.7)	91.0 (87.2 - 94.0)

Table 15. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response True*)	92.1 (88.4, 94.8)	93.7 (90.3, 96.1)	93.7 (90.3, 96.1)	95.3 (92.3 - 97.4)
7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response False*) [1]	78.5 (73.4, 83.0)	82.0 (77.2, 86.2)	83.7 (79.0, 87.7)	85.4 (80.9 - 89.2)
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response True*)	78.5 (73.4, 83.0)	82.7 (77.9, 86.8)	79.0 (73.9, 83.5)	80.7 (75.8 - 85.0)
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:				
11a	8 mg oral hydromorphone/day (*Correct Response True*)	N/A	79.0[2]	76.3[2]	78.7 (73.7 - 83.2)
11b	60 mg oral morphine/day (*Correct Response True*)	N/A	85.0[2]	84.7[2]	89.7 (85.7 - 92.9)
11c	30 mg oral oxycodone/day (*Correct Response True*)	N/A	71.3[2]	73.3[2]	77.1 (71.9 - 81.7)
11d	25 mcg transdermal fentanyl/hour (*Correct*	N/A	72.0[2]	74.3[2]	77.1 (71.9 - 81.7)

Table 15. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
	Response True)				
11e	25 mg oral oxymorphone/day (*Correct Response True*)	N/A	71.0[2]	71.0[2]	73.4 (68.1 - 78.3)
11f	An equianalgesic dose of another oral opioid (*Correct Response True*)	N/A	59.0[2]	59.0[2]	65.1 (59.4 - 70.5)
Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-the-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain					
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicine.				
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time (*Correct Response False*) [1]	N/A	65.3[2]	63.3[2]	69.1 (63.5 - 74.3)
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 (*Correct Response False*) [1]	N/A	74.7[2]	74.0[2]	82.1 (77.2 - 86.2)

Table 15. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
6c	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (*Correct Response True*)	N/A	N/A	N/A	41.9 (36.2 - 47.7)
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a	Acute or postoperative pain (*Correct Response No*)	78.1 (73.1, 82.7)	84.7 (80.1, 88.6)	86.7 (82.3, 90.3)	90.0 (86.1 - 93.2)
9b	Headache or migraine pain (*Correct Response No*)	89.1 (85.0, 92.4)	92.3 (88.7, 95.1)	90.7 (86.8, 93.7)	93.0 (89.5 - 95.6)
9c	Dental pain (*Correct Response No*)	94.7 (91.5, 96.9)	96.7 (94.0, 98.4)	97.0 (94.4, 98.6)	98.3 (96.2 - 99.5)
9d	Breakthrough pain from cancer (*Correct Response Yes*)	83.4 (78.8, 87.5)	89.3 (85.3, 92.6)	91.7 (87.9, 94.5)	92.0 (88.4 - 94.8)
9e	Chronic non-cancer pain (*Correct Response No*)	29.8[2]	47.0 (41.2, 52.8)	43.7 (38.0, 49.5)	50.8 (45.0 - 56.6)

Table 15. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, with Abuse Liability Similar to other Opioid Analgesics					
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True)*	97.7 (95.3, 99.1)	96.7 (94.0, 98.4)	96.0 (93.1, 97.9)	97.3 (94.8 - 98.8)
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a	A personal history of psychiatric illness (*Correct Response Yes*)	66.6 (60.9, 71.9)	72.0 (66.6, 77.0)	71.0 (65.5, 76.1)	75.4 (70.1 - 80.2)
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response Yes*)	99.7 (98.2, 100.0)	99.0 (97.1, 99.8)	99.3 (97.6, 99.9)	98.7 (96.6 - 99.6)
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
10a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response True*)	90.4 (86.5, 93.5)	94.0 (90.7, 96.4)	94.3 (91.1, 96.7)	95.7 (92.7 - 97.7)
Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration					
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
10b	TIRF medicines are	95.0	94.7	93.3	93.4

Table 15. Correct Response Rate Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
	interchangeable with each other regardless of route of administration (*Correct Response False*)	(91.9, 97.2)	(91.5, 96.9)	(89.9, 95.9)	(89.9 - 95.9)
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response True*)	92.7 (89.2, 95.4)	92.0 (88.3, 94.8)	93.0 (89.5, 95.6)	92.7 (89.1 - 95.4)
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response True*)	92.4 (88.8, 95.1)	91.3 (87.6, 94.3)	90.0 (86.0, 93.2)	92.7 (89.1 - 95.4)
13	Please answer True, False, or I don't know for each statement about TIRF medicines.				
13c	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product (*Correct Response False*)	95.7[2]	96.3[2]	97.7[2]	98.3 (96.2 - 99.5)

[1] Questions presented have been changed from previous survey waves.

[2] 95% confidence interval is not provided since the component was not part of a key risk message during reporting period.

Conclusions

In general, there is an overall trend over time toward maintaining, or even increasing, pharmacist knowledge and understanding of the key risk messages. The consistently high level of pharmacists' understanding of key risk messages in the latest (48-month) survey indicates that the Education Program for Pharmacists is meeting the goals of the TIRF REMS Access Program. Two exceptions where pharmacists scored low included understanding that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine, and that TIRF medicines are not indicated for chronic non-cancer pain, which may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

Appendix A Pharmacy Survey Protocol Track Change Document: Comparison of 36-month Survey to 48-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Actavis Laboratories FL, Inc.** **BioDelivery Sciences International, Inc. (BDSI)** ***(replaced Meda Pharmaceuticals on March 11, 2015)*** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **Galena Biopharma, Inc.** **Insys Therapeutics, Inc.** **Mallinckrodt Pharmaceuticals** ~~***Meda Pharmaceuticals***~~ **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**96.0**
DATE:	**12AUG2015**~~**18MAY2014**~~
APPROVED:	**FINAL**~~**Final**~~

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LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CATI	Computer-Assisted Telephone Interviewing
CSP	Closed System Pharmacy
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI) (replaced Meda Pharmaceuticals on March 11, 2015); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; ~~; Meda Pharmaceuticals;~~ Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS 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

An important component of the TIRF REMS is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI). This protocol will describe the administration of the surveys that will be conducted among pharmacists who are enrolled in the TIRF REMS Access Program.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists around the following key information and risk messages communicated through 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 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.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of pharmacists who are enrolled in the TIRF REMS Access Program. Respondents who have participated in a previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered via the Internet through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take up to 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the Knowledge, Attitudes~~Attitude~~, and Behavior (KAB) survey results for pharmacists included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions and to assess proposed revised wording to select questions. Qualitative research was performed in 2013 prior to Wave 2 of the survey. Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report,

4.1.2 Questions and Statements on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use “yes” or “no” as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- One question allowing for the respondent to list questions or comments.

Questionnaires will be analyzed to determine pharmacist understanding of each key risk message.

For statements or questions that use “true” or “yes” vs. “false” or “no” response options, the desired response for the key risk messages is generally “true” or “yes” indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are

formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired Response~~response~~**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**
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:	
11a	8 mg oral hydromorphone/day	**TRUE**
11b	60 mg oral morphine/day	**TRUE**
11c	30 mg oral oxycodone/day	**TRUE**
11d	25 mcg transdermal fentanyl/hour	**TRUE**
11e	25 mg oral oxymorphone/day	**TRUE**

11f	An equianalgesic dose of another oral opioid	**TRUE**

Key Risk Message 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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question No.	Question	Desired Response~~response~~
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
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**
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.	**FALSE**
6c	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	**TRUE**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**

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Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired Response~~response~~**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired Response~~response~~**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
13	Please answer True, False, or I don't know for each statement about TIRF medicines.	
13c	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	**FALSE**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program, receipt and understanding of the TIRF educational materials, and behaviors. The following question about behaviors will be asked after the key risk message questions.

Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of ~~"~~pharmacists~~ in charge"~~ from pharmacies that are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter to their pharmacy's "~~. Any~~ pharmacist in charge"~~ who works at an enrolled pharmacy may participate.~~ The text of the sample written invitation to pharmacists can be found in Appendix B.

If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of pharmacists will be randomly selected. The unique code provided in the invitation letter will be linked to the type of pharmacy (inpatient, outpatient, or Closed System Pharmacy [CSP]) in which the pharmacist works, based on the information provided as part of the TIRF REMS Access Program enrollment.

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All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium to thank them for their participation. The mailing will include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating pharmacists will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of pharmacies (e.g., chain and independent store) for participation.

Pharmacists will be offered Internet-based or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the Internet-based survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 pharmacists who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

Pharmacists who work at pharmacies that are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Pharmacists who have previously participated in the TIRF REMS KAB survey.
- Pharmacists or their immediate family members who have ever worked for Actavis Laboratories FL, Inc.; Anesta LLC; BioDelivery Sciences International, Inc. (BDSI);~~Anesta LLC;~~ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.;~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm pharmacist eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Pharmacist-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of pharmacists who do not have Internet access or prefer taking the survey over the telephone. It will also be convenient for pharmacists to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the pharmacist selects to participate in the survey via the Internet, he/she will be directed to a secured website where he/she will be instructed to complete screening questions. An Internet-based survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified time period when the Survey Coordinating Center is available.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to pharmacists
- The number of reminder letters issued to pharmacists
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who answered all questions presented to them
- Representativeness of pharmacists based on geography
- Description of survey participants, including:
    - Gender
    - Years of professional experience
    - How many times per month TIRF medicines dispensed in the last 6 months

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible pharmacists who completed all questions presented to them in the survey ("completers").

7.1.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of completers who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if they have questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $50 honorarium, a Thank You Letter, correct survey responses to key risk message questions, and the ISI after the survey is completed. Respondent contact information is also needed in the event that a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to dispense TIRF medicines.

Appendix A Pharmacist Questionnaire

Survey Legend

[PROGRAMMER] is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

(INTERVIEWER) is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

[ONLINE] indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

[BEGIN ~~ONLINE/PHONE~~ SURVEY CONTENT] and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

[TERMINATE] is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

> *Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.*

[RANDOMIZE LIST] is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

Response options for questions that allow multiple responses must be indicated with check boxes (□). At least one option must be selected for the question to be considered answered.

If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option.

Response options for questions that allow only one response must be indicated with radio buttons (○).

If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.

[GO TO Qx] (skip logic) is inserted after a response to indicate to the programmer that the

Survey Legend

survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

[FREE TEXT] indicates to the programmer that one line should be provided for data entry.

[MULTILINE INPUT] indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

[DROP-DOWN LIST INPUT WITH STATES TABLE] indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

Survey Legend

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
  West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[BEGIN ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; ~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[BEGIN PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.;~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have

questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Actavis Laboratories FL, Inc. **[TERMINATE]**
   - □ Anesta LLC **[TERMINATE]**
   - □ BioDelivery Sciences International, Inc. (BDSI) **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**

- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics, Inc. **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ ~~Meda Pharmaceuticals **[TERMINATE]**~~
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

   According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

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

[RANDOMIZE LIST]	True	False	I don't know
6a. According to the product labeling, a~~A~~ cancer patient may start~~can be started on~~ a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. According to the product labeling, a~~A~~ cancer patient who has been on an around-the-clock opioid for 1 day may~~can~~ start taking a TIRF medicine for breakthrough pain.	○	○	○
6c. A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	○	○	○
6d. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.	○	○	○

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

[RANDOMIZE LIST]	True	False	I don't know
7a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
7d. Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

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

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

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:

~~[RANDOMIZE LIST]~~	True	False	I don't know
11a. 8 mg oral hydromorphone/day	○	○	○
11b. 60 mg oral morphine/day	○	○	○
11c. 30 mg oral oxycodone/day	○	○	○
11d. 25 mcg transdermal fentanyl/hour	○	○	○
11e. 25 mg oral oxymorphone/day	○	○	○
11f. An equianalgesic dose of another oral opioid	○	○	○

12. How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
12a Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
12b Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
12c Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
12d Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
12e Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
12f. Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

13. Please answer True, False, or I don't know for each statement about TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
13a.	TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
13b.	All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.	○	○	○
13c.	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

14. **[INPATIENT PHARMACIST]** Does the inpatient pharmacy where you work have an established 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?

- ○ Yes
- ○ No
- ○ I don't know

15. **[OUTPATIENT PHARMACIST]** Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system?

- ○ Yes
- ○ No
- ○ I don't know

16. **[CSP OUTPATIENT PHARMACIST]** Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?

- ○ Yes
- ○ No
- ○ I don't know

17. **[INPATIENT PHARMACIST]** Please answer True, False, or I don't know for the following statement about TIRF medicines.

	True	**False**	**I don't know**
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	○	○	○

[BEGIN PREAMBLE 3]

The next set of questions is about the educational materials for TIRF medicines. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys®, and generic versions of any of these brands.

[END PREAMBLE 3]

18. Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q20]**
- ○ I don't know **[GO TO Q20]**

19. Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

20. Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q22]**
- ○ I don't know **[GO TO Q22]**

21. Did you read the Medication Guide for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No
- ○ I don't know

22. Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- ○ Yes
- ○ No **[GO TO DEMOGRAPHICS PREAMBLE-]**
- ○ I don't know **[GO TO DEMOGRAPHICS PREAMBLE]**

[IF QUESTION 22 = YES, DISPLAY ON SAME PAGE]

23. What are your questions? **[MULTILINE INPUT]**

[BEGIN DEMOGRAPHICS PREAMBLE 1 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

There are just a few more questions to help us combine your answers with other answers we have received.

[END DEMOGRAPHICS PREAMBLE 1]

24. Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?

- ○ Yes
- ○ No
- ○ I don't know

25. On average, how many times per month have you dispensed TIRF medicine within the last 6 months?

- ○ None **[Go to DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 – 2 times per month
- ○ 3 – 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

26. Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ ~~Onsolis®~~
- ☐ Subsys®

[BEGIN DEMOGRAPHICS PREAMBLE 2 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

These last few questions are for demographic purposes.

[END DEMOGRAPHICS PREAMBLE 2]

27. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

28. In total, how many years have you been a practicing pharmacist?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

29. In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE ~~ONLY:~~ BEGIN ADVERSE EVENT/PRODUCT COMPLAINT – KEEP ON ONE PAGE]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[BEGIN CLOSING 1 – KEEP ON ONE PAGE]

We would like to send you a $50 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- Yes
- No **[GO~~SKIP~~ TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[MUST BE 5 NUMERIC-ONLY CHARACTERS~~-ONLY~~]**

[END CLOSING 1]

[BEGIN
~~[~~CLOSING 2 – KEEP ON ONE PAGE]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- Yes
- No **[GO~~SKIP~~ TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC-ONLY CHARACTERS]**
[END CLOSING 2]

[BEGIN CLOSING 3]

That ends the survey. Thank you again for your help.

Formatted: Font: Bold

-[END CLOSING 3]

[END~~OF~~ SURVEY CONTENT]

Appendix B SAMPLE Pharmacist Invitation Letter

[CURR_DATE]

[PHARMACY_NAME]

[PHARMACY _STREET_ADDR]
[PHARMACY_CITY], [PHARMACY _STATE] [PHARMACY _ZIP]

[PHARMACY_FAX_NUMBER]

Dear [PHARMACIST_IN CHARGE]

Your Pharmacy was selected to receive this letter, because of enrollment in the TIRF REMS Access Program. We are contacting you to inform you about a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; ~~; Meda Pharmaceuticals;~~ Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

You are under no obligation to participate in this survey. Only one pharmacist from each enrolled pharmacy can participate. If you are interested in participating and to find out if you are eligible:

- Go to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**. ***We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.***

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

Appendix B Pharmacy Survey Listings and Stratified Analyses Tables

Table 1.1: Survey Administration Statistics

Parameter, n (%)	
Number of invitations distributed	4906
Number of invitations returned as undeliverable	45
Number of reminder letters distributed	4593
All Respondents[1]	607 (12.5)
Eligible Respondents[2]	334 (55.0)
Completed survey[3]	301 (90.1)
Did not complete the survey[3]	33 (9.9)
Respondents not eligible[2][4]	273 (45.0)

[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentages are based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Pharmacists (N=607) n (%)
Question 1: Do you agree to participate in this survey?	
Yes	426 (70.2)
No[1]	1 (0.2)
Discontinued	180 (29.7)
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.	
Yes[1]	9 (1.5)
No	365 (60.1)
I don't know[1]	52 (8.6)
Question not asked [2]	1 (0.2)
Discontinued	180 (29.7)
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access Program?	
Yes	338 (55.7)
No[1]	9 (1.5)
I don't know[1]	18 (3.0)
Question not asked [2]	62 (10.2)
Discontinued	180 (29.7)
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.	
Actavis Laboratories FL, Inc.[1]	1 (0.2)
Anesta, LLC[1]	0
BioDelivery Services International, Inc. (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	0
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	0
Mallinckrodt Pharmaceuticals[1]	2 (0.3)
McKesson Specialty Care Solutions[1]	0
Mylan, Inc.[1]	1 (0.2)

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Pharmacists (N=607) n (%)
Par Pharmaceutical, Inc.[1]	2 (0.3)
RelayHealth[1]	0
Teva Pharmaceuticals, Ltd.[1]	1 (0.2)
United BioSource Corporation[1]	0
FDA[1]	0
None of these apply[3]	334 (55.0)
I don't know[1]	2 (0.3)
Prefer not to answer[1]	0
Question not asked [2]	89 (14.7)
Discontinued	180 (29.7)

[1] Ineligible to participate in the survey.
[2] Question not asked due to previous termination response.
[3] Ineligible to participate in the survey if selected in addition to other responses.
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

Table 1.3: Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total
Summary Statistic (minutes)			
N	8	293	301
Mean (SD)	17.53 (2.755)	15.19 (8.913)	15.25 (8.812)
Minimum	15.3	4.7	4.7
Median	16.27	12.78	12.93
Maximum	21.5	68.4	68.4
Category, n			
0 to <5 Minutes	0	1	1
5 to <10 Minutes	0	97	97
10 to <15 Minutes	0	77	77
15 to <20 Minutes	6	58	64
20 to <25 Minutes	2	34	36
25 to <30 Minutes	0	9	9
30 Minutes or more	0	17	17

Table 2: Description of Eligible Pharmacists - Completed Surveys

Question	Pharmacists (N=301) n (%)
Question 24: Are you the Pharmacist in Charge for the TIRF REMS Access Program where you work?	
Yes	245 (81.4)
No	53 (17.6)
I don't know	3 (1.0)
Question 25: On average, how many times per month have you dispensed TIRF medicine within the last 6 months?	
None	118 (39.2)
1 - 2 times per month	112 (37.2)
3 - 5 times per month	25 (8.3)
More than 5 times per month	29 (9.6)
I don't remember	17 (5.6)
Question 26: Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.[1]	
Abstral®	12 (6.6)
Actiq® or generic Actiq®	117 (63.9)
Fentora®	63 (34.4)
Lazanda®	13 (7.1)
Subsys®	58 (31.7)
N/A (Answered "None" to Question 25)	118
Question 27: What is your gender?	
Male	192 (63.8)
Female	101 (33.6)
Prefer not to answer	8 (2.7)
Question 28: In total, how many years have you been a practicing pharmacist?	
Less than 3 years	17 (5.6)
3 - 5 years	33 (11.0)
6 - 10 years	51 (16.9)
11 - 15 years	36 (12.0)
More than 15 years	159 (52.8)

Table 2: Description of Eligible Pharmacists - Completed Surveys

Question	Pharmacists (N=301) n (%)
Prefer not to answer	5 (1.7)
Geographic Distribution (based on Question 29 - In which state do you practice?)[2]	
Northeast	71 (23.6)
Midwest	61 (20.3)
South	119 (39.5)
West	47 (15.6)
Other	1 (0.3)
Prefer not to answer	2 (0.7)

[1] Percentages are calculated based on the number of respondents to whom the question was presented.
[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=301) n (%)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[1]	279 (92.7)
False	22 (7.3)
I don't know	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	27 (9.0)
False[1]	263 (87.4)
I don't know	11 (3.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	44 (14.6)
False[1]	248 (82.4)
I don't know	9 (3.0)
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	70 (23.3)
False[1]	208 (69.1)
I don't know	23 (7.6)
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.	
True	37 (12.3)
False[1]	247 (82.1)
I don't know	17 (5.6)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[1]	126 (41.9)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=301) n (%)
False	136 (45.2)
I don't know	39 (13.0)
6d: Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.	
True	275 (91.4)
False	8 (2.7)
I don't know	18 (6.0)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[1]	274 (91.0)
False	19 (6.3)
I don't know	8 (2.7)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[1]	287 (95.3)
False	4 (1.3)
I don't know	10 (3.3)
7c: TIRF medicines may be used in opioid non-tolerant patients.	
True	35 (11.6)
False[1]	257 (85.4)
I don't know	9 (3.0)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[1]	243 (80.7)
False	45 (15.0)
I don't know	13 (4.3)
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[1]	293 (97.3)
False	7 (2.3)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=301) n (%)
I don't know	1 (0.3)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[1]	227 (75.4)
No	43 (14.3)
I don't know	31 (10.3)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[1]	297 (98.7)
No	2 (0.7)
I don't know	2 (0.7)
8c: A family history of asthma	
Yes	33 (11.0)
No	249 (82.7)
I don't know	19 (6.3)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	22 (7.3)
No[1]	271 (90.0)
I don't know	8 (2.7)
9b: Headache or migraine pain	
Yes	12 (4.0)
No[1]	280 (93.0)
I don't know	9 (3.0)
9c: Dental pain	
Yes	2 (0.7)
No[1]	296 (98.3)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=301) n (%)
I don't know	3 (1.0)
9d: Breakthrough pain from cancer	
Yes[1]	277 (92.0)
No	24 (8.0)
I don't know	0
9e: Chronic non-cancer pain	
Yes	131 (43.5)
No[1]	153 (50.8)
I don't know	17 (5.6)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[1]	288 (95.7)
False	8 (2.7)
I don't know	5 (1.7)
10b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	14 (4.7)
False[1]	281 (93.4)
I don't know	6 (2.0)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[1]	279 (92.7)
False	11 (3.7)
I don't know	11 (3.7)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[1]	279 (92.7)
False	14 (4.7)
I don't know	8 (2.7)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=301) n (%)
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:	
11a: 8 mg oral hydromorphone/day	
True[1]	237 (78.7)
False	30 (10.0)
I don't know	34 (11.3)
11b: 60 mg oral morphine/day	
True[1]	270 (89.7)
False	11 (3.7)
I don't know	20 (6.6)
11c: 30 mg oral oxycodone/day	
True[1]	232 (77.1)
False	41 (13.6)
I don't know	28 (9.3)
11d: 25 mcg transdermal fentanyl/hour	
True[1]	232 (77.1)
False	42 (14.0)
I don't know	27 (9.0)
11e: 25 mg oral oxymorphone/day	
True[1]	221 (73.4)
False	36 (12.0)
I don't know	44 (14.6)
11f: An equianalgesic dose of another oral opioid	
True[1]	196 (65.1)
False	49 (16.3)
I don't know	56 (18.6)
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.	
13a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=301) n (%)
True	7 (2.3)
False	279 (92.7)
I don't know	15 (5.0)
13b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.	
True	273 (90.7)
False	23 (7.6)
I don't know	5 (1.7)
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	
True	3 (1.0)
False[1]	296 (98.3)
I don't know	2 (0.7)

[1] Correct response.

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Pharmacists (N=301) n (%)
Question 18: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?	
Yes	299 (99.3)
No	0
I don't know	2 (0.7)
Question 19: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?[1]	
Yes	247 (82.6)
No	45 (15.1)
I don't know	7 (2.3)
N/A (Answered "No" or "I don't know" to Question 18)	2
Question 20: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?	
Yes	300 (99.7)
No	0
I don't know	1 (0.3)
Question 21: Did you read the Medication Guide for the TIRF medicine(s) that you dispense?[1]	
Yes	263 (87.7)
No	30 (10.0)
I don't know	7 (2.3)
N/A (Answered "No" or "I don't know" to Question 20)	1
Question 22: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?[2]	
Yes	5 (1.7)
No	283 (94.0)
I don't know	13 (4.3)

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim texts for question about the Medication Guide are presented in Listing 1.

Table 5: Responses to Questions about the Activities when Dispensing TIRF Medicines and Equipments in the Pharmacy - Completed Surveys

Question	Pharmacists (N=301) n (%)
Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
12a: Ask patients (or their caregivers) about the presence of children in the home	
Always	180 (59.8)
Only with the first prescription	67 (22.3)
Sometimes	36 (12.0)
Never	9 (3.0)
I don't know	9 (3.0)
12b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	
Always	235 (78.1)
Only with the first prescription	42 (14.0)
Sometimes	14 (4.7)
Never	6 (2.0)
I don't know	4 (1.3)
12c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	
Always	216 (71.8)
Only with the first prescription	48 (15.9)
Sometimes	27 (9.0)
Never	4 (1.3)
I don't know	6 (2.0)
12d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	
Always	238 (79.1)
Only with the first prescription	39 (13.0)
Sometimes	16 (5.3)
Never	4 (1.3)
I don't know	4 (1.3)
12e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	

Table 5: Responses to Questions about the Activities when Dispensing TIRF Medicines and Equipments in the Pharmacy - Completed Surveys

Question	Pharmacists (N=301) n (%)
Always	209 (69.4)
Only with the first prescription	66 (21.9)
Sometimes	20 (6.6)
Never	3 (1.0)
I don't know	3 (1.0)
12f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine	
Always	278 (92.4)
Only with the first prescription	14 (4.7)
Sometimes	4 (1.3)
Never	2 (0.7)
I don't know	3 (1.0)
Question 14: Does the inpatient pharmacy where you work have an established 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? (Inpatient Pharmacists, only)[1]	
Yes	8 (53.3)
No	7 (46.7)
I don't know	0
Question 15: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? (Outpatient Pharmacists, only)[1]	
Yes	262 (91.6)
No	10 (3.5)
I don't know	14 (4.9)
Question 16: Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center? (CSP Outpatient Pharmacists, only)[1]	
Yes	0
No	0
I don't know	0
Question 17: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient Pharmacists, only)[1]	

Table 5: Responses to Questions about the Activities when Dispensing TIRF Medicines and Equipments in the Pharmacy - Completed Surveys

Question	Pharmacists (N=301) n (%)
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	
True	0
False	13 (86.7)
I don't know	2 (13.3)

[1] Percentages are calculated based on the sample presented with this question.

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Pharmacists (N=301) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[2]	279 (92.7) [89.1 - 95.4]
False	22 (7.3)
I don't know	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	27 (9.0)
False[2]	263 (87.4) [83.1 - 90.9]
I don't know	11 (3.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	44 (14.6)
False[2]	248 (82.4) [77.6 - 86.5]
I don't know	9 (3.0)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[2]	274 (91.0) [87.2 - 94.0]
False	19 (6.3)
I don't know	8 (2.7)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[2]	287 (95.3) [92.3 - 97.4]
False	4 (1.3)
I don't know	10 (3.3)
7c: TIRF medicines may be used in opioid non-tolerant patients.	

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Pharmacists (N=301) n (%) [95% CI][1]
True	35 (11.6)
False[2]	257 (85.4) [80.9 - 89.2]
I don't know	9 (3.0)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[2]	243 (80.7) [75.8 - 85.0]
False	45 (15.0)
I don't know	13 (4.3)
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:	
11a: 8 mg oral hydromorphone/day	
True[2]	237 (78.7) [73.7 - 83.2]
False	30 (10.0)
I don't know	34 (11.3)
11b: 60 mg oral morphine/day	
True[2]	270 (89.7) [85.7 - 92.9]
False	11 (3.7)
I don't know	20 (6.6)
11c: 30 mg oral oxycodone/day	
True[2]	232 (77.1) [71.9 - 81.7]
False	41 (13.6)
I don't know	28 (9.3)
11d: 25 mcg transdermal fentanyl/hour	
True[2]	232 (77.1) [71.9 - 81.7]
False	42 (14.0)
I don't know	27 (9.0)

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Pharmacists (N=301) n (%) [95% CI][1]
11e: 25 mg oral oxymorphone/day	
True[2]	221 (73.4) [68.1 - 78.3]
False	36 (12.0)
I don't know	44 (14.6)
11f: An equianalgesic dose of another oral opioid	
True[2]	196 (65.1) [59.4 - 70.5]
False	49 (16.3)
I don't know	56 (18.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True[2]	15 (88.2) [63.6 - 98.5]	31 (93.9) [79.8 - 99.3]	80 (92.0) [84.1 - 96.7]	149 (93.7) [88.7 - 96.9]
False	2 (11.8)	2 (6.1)	7 (8.0)	10 (6.3)
I don't know	0	0	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
True	1 (5.9)	4 (12.1)	3 (3.4)	19 (11.9)
False[2]	16 (94.1) [71.3 - 99.9]	29 (87.9) [71.8 - 96.6]	79 (90.8) [82.7 - 95.9]	135 (84.9) [78.4 - 90.1]
I don't know	0	0	5 (5.7)	5 (3.1)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
True	0	5 (15.2)	15 (17.2)	24 (15.1)
False[2]	17 (100.0) [80.5 - 100.0]	28 (84.8) [68.1 - 94.9]	68 (78.2) [68.0 - 86.3]	131 (82.4) [75.6 - 88.0]
I don't know	0	0	4 (4.6)	4 (2.5)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
True[2]	16 (94.1) [71.3 - 99.9]	31 (93.9) [79.8 - 99.3]	78 (89.7) [81.3 - 95.2]	144 (90.6) [84.9 - 94.6]
False	0	0	7 (8.0)	12 (7.5)
I don't know	1 (5.9)	2 (6.1)	2 (2.3)	3 (1.9)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True[2]	17 (100.0) [80.5 - 100.0]	33 (100.0) [89.4 - 100.0]	84 (96.6) [90.3 - 99.3]	149 (93.7) [88.7 - 96.9]
False	0	0	1 (1.1)	3 (1.9)
I don't know	0	0	2 (2.3)	7 (4.4)
7c: TIRF medicines may be used in opioid non-tolerant patients.				
True	0	0	6 (6.9)	29 (18.2)
False[2]	15 (88.2) [63.6 - 98.5]	32 (97.0) [84.2 - 99.9]	81 (93.1) [85.6 - 97.4]	126 (79.2) [72.1 - 85.3]
I don't know	2 (11.8)	1 (3.0)	0	4 (2.5)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True[2]	14 (82.4) [56.6 - 96.2]	24 (72.7) [54.5 - 86.7]	71 (81.6) [71.9 - 89.1]	130 (81.8) [74.9 - 87.4]
False	2 (11.8)	8 (24.2)	14 (16.1)	21 (13.2)
I don't know	1 (5.9)	1 (3.0)	2 (2.3)	8 (5.0)

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
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:				
11a: 8 mg oral hydromorphone/day				
True[2]	11 (64.7) [38.3 - 85.8]	26 (78.8) [61.1 - 91.0]	66 (75.9) [65.5 - 84.4]	131 (82.4) [75.6 - 88.0]
False	2 (11.8)	1 (3.0)	12 (13.8)	15 (9.4)
I don't know	4 (23.5)	6 (18.2)	9 (10.3)	13 (8.2)
11b: 60 mg oral morphine/day				
True[2]	15 (88.2) [63.6 - 98.5]	28 (84.8) [68.1 - 94.9]	77 (88.5) [79.9 - 94.3]	146 (91.8) [86.4 - 95.6]
False	1 (5.9)	1 (3.0)	4 (4.6)	5 (3.1)
I don't know	1 (5.9)	4 (12.1)	6 (6.9)	8 (5.0)
11c: 30 mg oral oxycodone/day				
True[2]	12 (70.6) [44.0 - 89.7]	25 (75.8) [57.7 - 88.9]	65 (74.7) [64.3 - 83.4]	126 (79.2) [72.1 - 85.3]
False	4 (23.5)	3 (9.1)	14 (16.1)	20 (12.6)
I don't know	1 (5.9)	5 (15.2)	8 (9.2)	13 (8.2)
11d: 25 mcg transdermal fentanyl/hour				
True[2]	10 (58.8) [32.9 - 81.6]	22 (66.7) [48.2 - 82.0]	72 (82.8) [73.2 - 90.0]	125 (78.6) [71.4 - 84.7]

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
False	5 (29.4)	6 (18.2)	9 (10.3)	22 (13.8)
I don't know	2 (11.8)	5 (15.2)	6 (6.9)	12 (7.5)
11e: 25 mg oral oxymorphone/day				
True[2]	10 (58.8) [32.9 - 81.6]	26 (78.8) [61.1 - 91.0]	57 (65.5) [54.6 - 75.4]	125 (78.6) [71.4 - 84.7]
False	4 (23.5)	2 (6.1)	16 (18.4)	14 (8.8)
I don't know	3 (17.6)	5 (15.2)	14 (16.1)	20 (12.6)
11f: An equianalgesic dose of another oral opioid				
True[2]	10 (58.8) [32.9 - 81.6]	21 (63.6) [45.1 - 79.6]	58 (66.7) [55.7 - 76.4]	105 (66.0) [58.1 - 73.4]
False	4 (23.5)	4 (12.1)	19 (21.8)	22 (13.8)
I don't know	3 (17.6)	8 (24.2)	10 (11.5)	32 (20.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:					
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer					
True[2]	110 (93.2) [87.1 - 97.0]	104 (92.9) [86.4 - 96.9]	24 (96.0) [79.6 - 99.9]	26 (89.7) [72.6 - 97.8]	15 (88.2) [63.6 - 98.5]
False	8 (6.8)	8 (7.1)	1 (4.0)	3 (10.3)	2 (11.8)
I don't know	0	0	0	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before					
True	8 (6.8)	11 (9.8)	4 (16.0)	1 (3.4)	3 (17.6)
False[2]	106 (89.8) [82.9 - 94.6]	95 (84.8) [76.8 - 90.9]	21 (84.0) [63.9 - 95.5]	27 (93.1) [77.2 - 99.2]	14 (82.4) [56.6 - 96.2]
I don't know	4 (3.4)	6 (5.4)	0	1 (3.4)	0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy					
True	10 (8.5)	20 (17.9)	7 (28.0)	5 (17.2)	2 (11.8)
False[2]	105 (89.0) [81.9 - 94.0]	88 (78.6) [69.8 - 85.8]	18 (72.0) [50.6 - 87.9]	23 (79.3) [60.3 - 92.0]	14 (82.4) [56.6 - 96.2]
I don't know	3 (2.5)	4 (3.6)	0	1 (3.4)	1 (5.9)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.					
True[2]	103 (87.3) [79.9 - 92.7]	106 (94.6) [88.7 - 98.0]	21 (84.0) [63.9 - 95.5]	27 (93.1) [77.2 - 99.2]	17 (100.0) [80.5 - 100.0]
False	12 (10.2)	2 (1.8)	3 (12.0)	2 (6.9)	0
I don't know	3 (2.5)	4 (3.6)	1 (4.0)	0	0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.					
True[2]	115 (97.5) [92.7 - 99.5]	105 (93.8) [87.5 - 97.5]	24 (96.0) [79.6 - 99.9]	28 (96.6) [82.2 - 99.9]	15 (88.2) [63.6 - 98.5]
False	0	2 (1.8)	0	1 (3.4)	1 (5.9)
I don't know	3 (2.5)	5 (4.5)	1 (4.0)	0	1 (5.9)
7c: TIRF medicines may be used in opioid non-tolerant patients.					
True	18 (15.3)	9 (8.0)	5 (20.0)	2 (6.9)	1 (5.9)
False[2]	96 (81.4) [73.1 - 87.9]	100 (89.3) [82.0 - 94.3]	19 (76.0) [54.9 - 90.6]	27 (93.1) [77.2 - 99.2]	15 (88.2) [63.6 - 98.5]
I don't know	4 (3.4)	3 (2.7)	1 (4.0)	0	1 (5.9)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.					
True[2]	91 (77.1) [68.5 - 84.3]	93 (83.0) [74.8 - 89.5]	19 (76.0) [54.9 - 90.6]	24 (82.8) [64.2 - 94.2]	16 (94.1) [71.3 - 99.9]

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
False	21 (17.8)	14 (12.5)	5 (20.0)	4 (13.8)	1 (5.9)
I don't know	6 (5.1)	5 (4.5)	1 (4.0)	1 (3.4)	0
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:					
11a: 8 mg oral hydromorphone/day					
True[2]	91 (77.1) [68.5 - 84.3]	87 (77.7) [68.8 - 85.0]	18 (72.0) [50.6 - 87.9]	26 (89.7) [72.6 - 97.8]	15 (88.2) [63.6 - 98.5]
False	9 (7.6)	15 (13.4)	3 (12.0)	3 (10.3)	0
I don't know	18 (15.3)	10 (8.9)	4 (16.0)	0	2 (11.8)
11b: 60 mg oral morphine/day					
True[2]	102 (86.4) [78.9 - 92.0]	103 (92.0) [85.3 - 96.3]	22 (88.0) [68.8 - 97.5]	28 (96.6) [82.2 - 99.9]	15 (88.2) [63.6 - 98.5]
False	6 (5.1)	2 (1.8)	1 (4.0)	1 (3.4)	1 (5.9)
I don't know	10 (8.5)	7 (6.3)	2 (8.0)	0	1 (5.9)
11c: 30 mg oral oxycodone/day					
True[2]	88 (74.6) [65.7 - 82.1]	87 (77.7) [68.8 - 85.0]	14 (56.0) [34.9 - 75.6]	27 (93.1) [77.2 - 99.2]	16 (94.1) [71.3 - 99.9]
False	17 (14.4)	15 (13.4)	6 (24.0)	2 (6.9)	1 (5.9)

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
I don't know	13 (11.0)	10 (8.9)	5 (20.0)	0	0
11d: 25 mcg transdermal fentanyl/hour					
True[2]	90 (76.3) [67.6 - 83.6]	87 (77.7) [68.8 - 85.0]	16 (64.0) [42.5 - 82.0]	25 (86.2) [68.3 - 96.1]	14 (82.4) [56.6 - 96.2]
False	16 (13.6)	15 (13.4)	5 (20.0)	4 (13.8)	2 (11.8)
I don't know	12 (10.2)	10 (8.9)	4 (16.0)	0	1 (5.9)
11e: 25 mg oral oxymorphone/day					
True[2]	84 (71.2) [62.1 - 79.2]	81 (72.3) [63.1 - 80.4]	16 (64.0) [42.5 - 82.0]	27 (93.1) [77.2 - 99.2]	13 (76.5) [50.1 - 93.2]
False	14 (11.9)	19 (17.0)	1 (4.0)	2 (6.9)	0
I don't know	20 (16.9)	12 (10.7)	8 (32.0)	0	4 (23.5)
11f: An equianalgesic dose of another oral opioid					
True[2]	76 (64.4) [55.1 - 73.0]	68 (60.7) [51.0 - 69.8]	16 (64.0) [42.5 - 82.0]	22 (75.9) [56.5 - 89.7]	14 (82.4) [56.6 - 96.2]
False	18 (15.3)	21 (18.8)	4 (16.0)	5 (17.2)	1 (5.9)
I don't know	24 (20.3)	23 (20.5)	5 (20.0)	2 (6.9)	2 (11.8)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Correct Responses	Pharmacists (N=301) n (%) [95% CI][1]
0 correct responses	0
1 correct response	1 (0.3)
2 correct responses	1 (0.3)
3 correct responses	2 (0.7)
4 correct responses	4 (1.3)
5 correct responses	5 (1.7)
6 correct responses	9 (3.0)
7 correct responses	13 (4.3)
8 correct responses	11 (3.7)
9 correct responses	30 (10.0)
10 correct responses	33 (11.0)
11 correct responses	37 (12.3)
12 correct responses	66 (21.9)
13 correct responses	89 (29.6) [24.5 - 35.1]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Pharmacists (N=301) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	70 (23.3)
False[2]	208 (69.1) [63.5 - 74.3]
I don't know	23 (7.6)
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.	
True	37 (12.3)
False[2]	247 (82.1) [77.2 - 86.2]
I don't know	17 (5.6)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[2]	126 (41.9) [36.2 - 47.7]
False	136 (45.2)
I don't know	39 (13.0)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	22 (7.3)
No[2]	271 (90.0) [86.1 - 93.2]
I don't know	8 (2.7)
9b: Headache or migraine pain	
Yes	12 (4.0)

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Pharmacists (N=301) n (%) [95% CI][1]
No[2]	280 (93.0) [89.5 - 95.6]
I don't know	9 (3.0)
9c: Dental pain	
Yes	2 (0.7)
No[2]	296 (98.3) [96.2 - 99.5]
I don't know	3 (1.0)
9d: Breakthrough pain from cancer	
Yes[2]	277 (92.0) [88.4 - 94.8]
No	24 (8.0)
I don't know	0
9e: Chronic non-cancer pain	
Yes	131 (43.5)
No[2]	153 (50.8) [45.0 - 56.6]
I don't know	17 (5.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.				
True	2 (11.8)	4 (12.1)	17 (19.5)	45 (28.3)
False[2]	14 (82.4) [56.6 - 96.2]	27 (81.8) [64.5 - 93.0]	64 (73.6) [63.0 - 82.4]	103 (64.8) [56.8 - 72.2]
I don't know	1 (5.9)	2 (6.1)	6 (6.9)	11 (6.9)
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.				
True	2 (11.8)	2 (6.1)	6 (6.9)	27 (17.0)
False[2]	13 (76.5) [50.1 - 93.2]	30 (90.9) [75.7 - 98.1]	76 (87.4) [78.5 - 93.5]	125 (78.6) [71.4 - 84.7]
I don't know	2 (11.8)	1 (3.0)	5 (5.7)	7 (4.4)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	10 (58.8) [32.9 - 81.6]	17 (51.5) [33.5 - 69.2]	34 (39.1) [28.8 - 50.1]	64 (40.3) [32.6 - 48.3]
False	6 (35.3)	7 (21.2)	40 (46.0)	82 (51.6)
I don't know	1 (5.9)	9 (27.3)	13 (14.9)	13 (8.2)

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
Yes	2 (11.8)	1 (3.0)	5 (5.7)	13 (8.2)
No[2]	15 (88.2) [63.6 - 98.5]	31 (93.9) [79.8 - 99.3]	78 (89.7) [81.3 - 95.2]	143 (89.9) [84.2 - 94.1]
I don't know	0	1 (3.0)	4 (4.6)	3 (1.9)
9b: Headache or migraine pain				
Yes	0	2 (6.1)	2 (2.3)	8 (5.0)
No[2]	16 (94.1) [71.3 - 99.9]	29 (87.9) [71.8 - 96.6]	83 (95.4) [88.6 - 98.7]	147 (92.5) [87.2 - 96.0]
I don't know	1 (5.9)	2 (6.1)	2 (2.3)	4 (2.5)
9c: Dental pain				
Yes	0	0	0	2 (1.3)
No[2]	17 (100.0) [80.5 - 100.0]	32 (97.0) [84.2 - 99.9]	86 (98.9) [93.8 - 100.0]	156 (98.1) [94.6 - 99.6]
I don't know	0	1 (3.0)	1 (1.1)	1 (0.6)
9d: Breakthrough pain from cancer				

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
Yes[2]	15 (88.2) [63.6 - 98.5]	29 (87.9) [71.8 - 96.6]	83 (95.4) [88.6 - 98.7]	145 (91.2) [85.7 - 95.1]
No	2 (11.8)	4 (12.1)	4 (4.6)	14 (8.8)
I don't know	0	0	0	0
9e: Chronic non-cancer pain				
Yes	9 (52.9)	14 (42.4)	31 (35.6)	76 (47.8)
No[2]	8 (47.1) [23.0 - 72.2]	15 (45.5) [28.1 - 63.6]	48 (55.2) [44.1 - 65.9]	78 (49.1) [41.1 - 57.1]
I don't know	0	4 (12.1)	8 (9.2)	5 (3.1)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.					
True	24 (20.3)	23 (20.5)	9 (36.0)	9 (31.0)	5 (29.4)
False[2]	82 (69.5) [60.3 - 77.6]	82 (73.2) [64.0 - 81.1]	13 (52.0) [31.3 - 72.2]	19 (65.5) [45.7 - 82.1]	12 (70.6) [44.0 - 89.7]
I don't know	12 (10.2)	7 (6.3)	3 (12.0)	1 (3.4)	0
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.					
True	11 (9.3)	16 (14.3)	3 (12.0)	5 (17.2)	2 (11.8)
False[2]	99 (83.9) [76.0 - 90.0]	90 (80.4) [71.8 - 87.3]	21 (84.0) [63.9 - 95.5]	23 (79.3) [60.3 - 92.0]	14 (82.4) [56.6 - 96.2]
I don't know	8 (6.8)	6 (5.4)	1 (4.0)	1 (3.4)	1 (5.9)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.					
True[2]	47 (39.8) [30.9 - 49.3]	48 (42.9) [33.5 - 52.6]	8 (32.0) [14.9 - 53.5]	16 (55.2) [35.7 - 73.6]	7 (41.2) [18.4 - 67.1]
False	49 (41.5)	52 (46.4)	15 (60.0)	12 (41.4)	8 (47.1)
I don't know	22 (18.6)	12 (10.7)	2 (8.0)	1 (3.4)	2 (11.8)

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.					
9a: Acute or postoperative pain					
Yes	5 (4.2)	9 (8.0)	3 (12.0)	3 (10.3)	2 (11.8)
No[2]	111 (94.1) [88.2 - 97.6]	98 (87.5) [79.9 - 93.0]	21 (84.0) [63.9 - 95.5]	26 (89.7) [72.6 - 97.8]	15 (88.2) [63.6 - 98.5]
I don't know	2 (1.7)	5 (4.5)	1 (4.0)	0	0
9b: Headache or migraine pain					
Yes	2 (1.7)	7 (6.3)	1 (4.0)	2 (6.9)	0
No[2]	113 (95.8) [90.4 - 98.6]	103 (92.0) [85.3 - 96.3]	22 (88.0) [68.8 - 97.5]	25 (86.2) [68.3 - 96.1]	17 (100.0) [80.5 - 100.0]
I don't know	3 (2.5)	2 (1.8)	2 (8.0)	2 (6.9)	0
9c: Dental pain					
Yes	1 (0.8)	1 (0.9)	0	0	0
No[2]	116 (98.3) [94.0 - 99.8]	109 (97.3) [92.4 - 99.4]	25 (100.0) [86.3 - 100.0]	29 (100.0) [88.1 - 100.0]	17 (100.0) [80.5 - 100.0]
I don't know	1 (0.8)	2 (1.8)	0	0	0

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
9d: Breakthrough pain from cancer					
Yes[2]	108 (91.5) [85.0 - 95.9]	103 (92.0) [85.3 - 96.3]	22 (88.0) [68.8 - 97.5]	27 (93.1) [77.2 - 99.2]	17 (100.0) [80.5 - 100.0]
No	10 (8.5)	9 (8.0)	3 (12.0)	2 (6.9)	0
I don't know	0	0	0	0	0
9e: Chronic non-cancer pain					
Yes	50 (42.4)	47 (42.0)	16 (64.0)	12 (41.4)	6 (35.3)
No[2]	58 (49.2) [39.8 - 58.5]	61 (54.5) [44.8 - 63.9]	8 (32.0) [14.9 - 53.5]	16 (55.2) [35.7 - 73.6]	10 (58.8) [32.9 - 81.6]
I don't know	10 (8.5)	4 (3.6)	1 (4.0)	1 (3.4)	1 (5.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Correct Responses	Pharmacists (N=301) n (%) [95% CI][1]
0 correct responses	0
1 correct response	2 (0.7)
2 correct responses	2 (0.7)
3 correct responses	11 (3.7)
4 correct responses	26 (8.6)
5 correct responses	49 (16.3)
6 correct responses	74 (24.6)
7 correct responses	70 (23.3)
8 correct responses	67 (22.3) [17.7 - 27.4]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Question	Pharmacists (N=301) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[2]	293 (97.3) [94.8 - 98.8]
False	7 (2.3)
I don't know	1 (0.3)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[2]	227 (75.4) [70.1 - 80.2]
No	43 (14.3)
I don't know	31 (10.3)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[2]	297 (98.7) [96.6 - 99.6]
No	2 (0.7)
I don't know	2 (0.7)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[2]	288 (95.7) [92.7 - 97.7]
False	8 (2.7)
I don't know	5 (1.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True[2]	17 (100.0) [80.5 - 100.0]	33 (100.0) [89.4 - 100.0]	86 (98.9) [93.8 - 100.0]	152 (95.6) [91.1 - 98.2]
False	0	0	1 (1.1)	6 (3.8)
I don't know	0	0	0	1 (0.6)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes[2]	16 (94.1) [71.3 - 99.9]	29 (87.9) [71.8 - 96.6]	71 (81.6) [71.9 - 89.1]	108 (67.9) [60.1 - 75.1]
No	0	4 (12.1)	6 (6.9)	33 (20.8)
I don't know	1 (5.9)	0	10 (11.5)	18 (11.3)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes[2]	17 (100.0) [80.5 - 100.0]	33 (100.0) [89.4 - 100.0]	86 (98.9) [93.8 - 100.0]	156 (98.1) [94.6 - 99.6]
No	0	0	0	2 (1.3)
I don't know	0	0	1 (1.1)	1 (0.6)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True[2]	16 (94.1) [71.3 - 99.9]	31 (93.9) [79.8 - 99.3]	83 (95.4) [88.6 - 98.7]	153 (96.2) [92.0 - 98.6]
False	0	1 (3.0)	2 (2.3)	5 (3.1)
I don't know	1 (5.9)	1 (3.0)	2 (2.3)	1 (0.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.					
True[2]	115 (97.5) [92.7 - 99.5]	107 (95.5) [89.9 - 98.5]	25 (100.0) [86.3 - 100.0]	29 (100.0) [88.1 - 100.0]	17 (100.0) [80.5 - 100.0]
False	2 (1.7)	5 (4.5)	0	0	0
I don't know	1 (0.8)	0	0	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.					
8a: A personal history of psychiatric illness					
Yes[2]	90 (76.3) [67.6 - 83.6]	89 (79.5) [70.8 - 86.5]	17 (68.0) [46.5 - 85.1]	20 (69.0) [49.2 - 84.7]	11 (64.7) [38.3 - 85.8]
No	14 (11.9)	14 (12.5)	7 (28.0)	5 (17.2)	3 (17.6)
I don't know	14 (11.9)	9 (8.0)	1 (4.0)	4 (13.8)	3 (17.6)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse					
Yes[2]	116 (98.3) [94.0 - 99.8]	111 (99.1) [95.1 - 100.0]	25 (100.0) [86.3 - 100.0]	28 (96.6) [82.2 - 99.9]	17 (100.0) [80.5 - 100.0]
No	0	1 (0.9)	0	1 (3.4)	0
I don't know	2 (1.7)	0	0	0	0

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.					
True[2]	113 (95.8) [90.4 - 98.6]	110 (98.2) [93.7 - 99.8]	22 (88.0) [68.8 - 97.5]	27 (93.1) [77.2 - 99.2]	16 (94.1) [71.3 - 99.9]
False	3 (2.5)	2 (1.8)	1 (4.0)	2 (6.9)	0
I don't know	2 (1.7)	0	2 (8.0)	0	1 (5.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Correct Responses	Pharmacists (N=301) n (%) [95% CI][1]
0 correct responses	0
1 correct response	0
2 correct responses	6 (2.0)
3 correct responses	87 (28.9)
4 correct responses	208 (69.1) [63.5 - 74.3]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Pharmacists (N=301) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	14 (4.7)
False[2]	281 (93.4) [89.9 - 95.9]
I don't know	6 (2.0)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[2]	279 (92.7) [89.1 - 95.4]
False	11 (3.7)
I don't know	11 (3.7)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[2]	279 (92.7) [89.1 - 95.4]
False	14 (4.7)
I don't know	8 (2.7)
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.	
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	
True	3 (1.0)
False[2]	296 (98.3) [96.2 - 99.5]
I don't know	2 (0.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.3: Responses to Questions Linked to Key Risk Message #4 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
True	0	1 (3.0)	5 (5.7)	8 (5.0)
False[2]	17 (100.0) [80.5 - 100.0]	31 (93.9) [79.8 - 99.3]	80 (92.0) [84.1 - 96.7]	148 (93.1) [88.0 - 96.5]
I don't know	0	1 (3.0)	2 (2.3)	3 (1.9)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True[2]	15 (88.2) [63.6 - 98.5]	32 (97.0) [84.2 - 99.9]	81 (93.1) [85.6 - 97.4]	146 (91.8) [86.4 - 95.6]
False	2 (11.8)	0	2 (2.3)	7 (4.4)
I don't know	0	1 (3.0)	4 (4.6)	6 (3.8)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True[2]	16 (94.1) [71.3 - 99.9]	31 (93.9) [79.8 - 99.3]	82 (94.3) [87.1 - 98.1]	145 (91.2) [85.7 - 95.1]
False	0	1 (3.0)	3 (3.4)	10 (6.3)
I don't know	1 (5.9)	1 (3.0)	2 (2.3)	4 (2.5)
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.				
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.				

Table 9.1.3: Responses to Questions Linked to Key Risk Message #4 by Time Practicing as Pharmacist - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Time Practicing as Pharmacist			
	Less than 3 years (N=17) n (%) [95% CI][1]	3 to 5 years (N=33) n (%) [95% CI][1]	6 to 15 years (N=87) n (%) [95% CI][1]	More than 15 years (N=159) n (%) [95% CI][1]
True	0	1 (3.0)	1 (1.1)	1 (0.6)
False[2]	17 (100.0) [80.5 - 100.0]	32 (97.0) [84.2 - 99.9]	86 (98.9) [93.8 - 100.0]	156 (98.1) [94.6 - 99.6]
I don't know	0	0	0	2 (1.3)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.4: Responses to Questions Linked to Key Risk Message #4 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
10b: TIRF medicines are interchangeable with each other regardless of route of administration.					
True	5 (4.2)	4 (3.6)	1 (4.0)	2 (6.9)	2 (11.8)
False[2]	110 (93.2) [87.1 - 97.0]	105 (93.8) [87.5 - 97.5]	24 (96.0) [79.6 - 99.9]	27 (93.1) [77.2 - 99.2]	15 (88.2) [63.6 - 98.5]
I don't know	3 (2.5)	3 (2.7)	0	0	0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.					
True[2]	109 (92.4) [86.0 - 96.5]	104 (92.9) [86.4 - 96.9]	25 (100.0) [86.3 - 100.0]	25 (86.2) [68.3 - 96.1]	16 (94.1) [71.3 - 99.9]
False	5 (4.2)	3 (2.7)	0	2 (6.9)	1 (5.9)
I don't know	4 (3.4)	5 (4.5)	0	2 (6.9)	0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.					
True[2]	109 (92.4) [86.0 - 96.5]	105 (93.8) [87.5 - 97.5]	21 (84.0) [63.9 - 95.5]	27 (93.1) [77.2 - 99.2]	17 (100.0) [80.5 - 100.0]
False	5 (4.2)	5 (4.5)	3 (12.0)	1 (3.4)	0
I don't know	4 (3.4)	2 (1.8)	1 (4.0)	1 (3.4)	0
Question 13: Please answer True, False, or I don't know for each statement about TIRF medicines.					

Table 9.1.4: Responses to Questions Linked to Key Risk Message #4 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=118) n (%) [95% CI][1]	1 - 2 times per month (N=112) n (%) [95% CI][1]	3 - 5 times per month (N=25) n (%) [95% CI][1]	More than 5 times per month (N=29) n (%) [95% CI][1]	I don't remember (N=17) n (%) [95% CI][1]
13c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.					
True	2 (1.7)	0	1 (4.0)	0	0
False[2]	116 (98.3) [94.0 - 99.8]	110 (98.2) [93.7 - 99.8]	24 (96.0) [79.6 - 99.9]	29 (100.0) [88.1 - 100.0]	17 (100.0) [80.5 - 100.0]
I don't know	0	2 (1.8)	0	0	0

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Correct Responses	Pharmacists (N=301) n (%) [95% CI][1]
0 correct responses	0
1 correct response	2 (0.7)
2 correct responses	7 (2.3)
3 correct responses	49 (16.3)
4 correct responses	243 (80.7) [75.8 - 85.0]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Listing 1: Listing of Verbatim Responses to Question #27 (Questions about the Full Prescribing Information or the Medication Guide) - Completed Surveys

Verbatim Responses
EACH DRUG REQUIRES A SOURCE CHECK
Exact route of administration - apparently, one of my patients complained that theproduct 'leaked'. I was trying to get info to verify or dispute that claim.
I LIKE TO GET PICTURE PRESENTATION ON THIS SO WE CAN HELP CUSTOMER ABOUT THIS DRUG
The full prescribing information is confusing for each product. The FDA should consider harmonizing the prescribing information for all medications in this same class
The notification system for TIRFs is a little hard to understand, have done test claims but to do an actual claim didn't seem to be addressed.

Listing 2: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
Exact route of administration - apparently, one of my patients complained that theproduct "leaked". I was trying to get info to verify or dispute that claim.	Internet
The notification system for TIRFs is a little hard to understand, have done test claims but to do an actual claim didn't seem to be addressed.	Internet
The full prescribing information is confusing for each product. The FDA should consider harmonizing the prescribing information for all medications in this same class	Internet

12.7.3 Prescriber KAB Survey

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior (KAB) about TIRF Products' Safety and Use Information**
Document Number	Wave 4, 48-month REMS Assessment Version 1.0
Survey Time Period	31 August 2015 to 16 October 2015
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies**: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. (BDSI) Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Galena Biopharma, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc.
Date:	15 December 2015

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE/PC PSP	Adverse Event/Product Complaint Project Specific Procedure
BDSI	BioDelivery Sciences International, Inc.
CI	Confidence Interval
DoD	Department of Defense
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
N/A	Not Applicable
NIH	National Institutes of Health
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SD	Standard Deviation
SCC	Survey Coordinating Center
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access Program	REMS Program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service
VA	Department of Veterans Affairs

Executive Summary

The 48-month Knowledge, Attitudes, and Behavior (KAB) survey for prescribers who prescribe Transmucosal Immediate Release Fentanyl (TIRF) medicines was conducted as part of the 48-Month TIRF Risk Evaluation and Mitigation Strategy (REMS) Access Program Assessment. The survey launched on 31 August 2015 and closed on 16 October 2015. Food and Drug Administration (FDA) feedback was provided in the 24-month and 36-month Assessment Report Acknowledgement Letter and where applicable these changes were implemented in the 48-month survey. Changes included adding questions on whether the respondent works in a closed system, and for respondents who stated they prescribe TIRF medicines for chronic non-cancer pain addressing why they feel that this is an appropriate use of TIRF medicines, removing 'Onsolis' as a response option throughout the survey because it is no longer available, moving specified existing survey questions under key risk messages, removing Question 19 (*Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?*), and including an analysis of demographics of the prescriber survey respondents compared to the demographics of the general population of TIRF prescribers.

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed. The survey also included questions about whether prescribers received, read, understood, and used the product-specific educational materials, and included questions about compliance with the REMS requirements.

Invitations (and reminders) were sent to a random sample of prescribers who prescriber TIRF products, were known to have received the REMS educational materials, and who were enrolled in the TIRF REMS Access Program as of 30 June 2015. From the total of 587 respondents who accessed the survey, 350 (59.6%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (88.6%) completed the survey, exceeding the target of 300 completed surveys. The geographic distribution of survey respondents was similar to the overall population of prescribers who prescribe TIRF medicines (comparison requested by FDA).

In general, there is an overall trend across all prescriber KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys) toward increasing improvement in prescriber knowledge and understanding of the key risk messages. Of the 31 components included as part of key risk messages, 21 components of the key risk messages had a correct response rate >80% and 9 components had a correct response rate between 67.7% and 78.7%. For Component 9e, 201 prescribers (64.8%) indicated they do not prescribe TIRF medicines for chronic non-cancer pain. The 34.2% of prescribers who stated they do prescribe TIRF medicines for chronic non-cancer pain were presented with 2 additional questions as requested by the FDA; the type of chronic pain conditions they prescribe a TIRF medicine to

treat, and the reasons for selecting a TIRF medicine to treat these conditions. Based on prescriber responses, and the high percentage of respondents who indicated they received and read the REMS educational materials, the responses may reflect behavior more than knowledge. That is, prescribers are aware of the labeled indication but choose to prescribe off-label for certain patients.

The consistently high level of prescriber understanding of key risk messages in the latest (48-month) survey indicates that the Education Program for Prescribers is meeting the goals of the TIRF REMS Access Program. The TRIG will evaluate the concepts that have scored low among stakeholders to determine if any action is warranted. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

1. PRESCRIBER SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines are a class of immediate-release opioid analgesics indicated for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The FDA has determined that a shared system REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program was approved by the FDA on 28 December 2011. This report describes the results from the prescriber surveys conducted for the 48-Month TIRF REMS Access Program Assessment, and reflects the reporting period of 29 October 2014 to 28 October 2015. The 48-month Knowledge, Attitudes, and Behavior (KAB) survey launched on 31 August 2015 and closed on 16 October 2015.

The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and their generic equivalents. The TRIG includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan, Inc.; and Par Pharmaceutical, Inc. Two companies joined the TRIG during the reporting period: Actavis Laboratories FL, Inc. joined on 6 February 2015 and BDSI replaced Meda Pharmaceuticals on 11 March 2015.

The TIRF REMS Access Program consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. 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 the following:

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.

An important component of the TIRF REMS Access Program Assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS Access Program educational materials, enrollment form, and Prescribing Information of each product. Administration of the surveys conducted among prescribers who are enrolled in the TIRF REMS Access Program is described in the protocol (See Appendix A). Note: Protocol and survey question revisions from the 36-month assessment report are identified as tracked changes.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

1.1 Changes to the KAB Survey for Prescribers Based on FDA Feedback

FDA feedback was received on the KAB survey for prescribers in the 24-month and the 36-month FDA REMS Acknowledgement Letters.

The FDA provided the following feedback to the TRIG on the KAB survey for prescribers based on results included in the 24-month REMS Assessment Report.

- In the prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

- In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

This feedback was provided after the launch of the 36-month KAB survey for prescribers, thus the changes were incorporated into the 48-month KAB survey for prescribers and results from the revised survey are included in this 48-month KAB Assessment Report.

The FDA provided the following feedback to the TRIG on the KAB survey for prescribers based on results included in the 36-month REMS Assessment Report:

- Remove Onsolis as a response option throughout the survey as it is no longer available

- Move existing survey questions (Question 7b, Question 11a-f) into Key Risk Message 1
- Move existing survey question (Question 6a, 6b, 18b, 18c) into Key Risk Message 2
- Move an existing survey question (Question 10d) into Key Risk Message 4
- Remove Question 19
- Include an analysis of demographics of the prescriber survey respondents compared to the demographics of the general population of TIRF prescribers

The 36-month Assessment Report Acknowledgement Letter was received by the TRIG sponsors on 04 August 2015. All but one of the requested changes were incorporated into the 48-month KAB survey prior to launch. In order to incorporate FDA's feedback in the 48-month Prescriber KAB survey, the survey launch date originally scheduled for the second week of August was delayed until 31 August 2015.

The remaining FDA request was to provide an analysis of how the demographics of the prescriber survey respondents compare to the demographics of the general population of TIRF prescribers. Due to timing of the request and the time required to obtain these data, this information was unable to be included in the 48-Month FDA Assessment Report. As communicated to FDA on 09 September 2015, the TRIG plans to submit a Supplemental Report to FDA to include items that were unable to be included in this assessment report based on the timing of the 36-Month FDA Assessment Report Acknowledgement Letter. A comparison of geographic data between survey respondents and the general population of TIRF prescribers are included in this report; the full demographic comparison will be included in the Supplemental Report estimated to be delivered on May 4, 2016.

2. PRESCRIBER SURVEY OBJECTIVES

The evaluation survey uses a questionnaire to document the level of knowledge and assess the attitudes and behaviors of prescribers regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are 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.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey also collects data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions developed to test prescriber understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Sample

A sample of 300 prescribers who prescribe TIRF products and were known to have received the REMS educational materials was planned for this fourth KAB survey which was expected to be open from 31 August 2015 to 20 October 2015. The survey sample size was determined based on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Subjects were recruited from a random sample of prescribers who were enrolled in the TIRF REMS Access Program as of 30 June 2015. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, RelayHealth, McKesson Specialty Care Solutions, United BioSource Corporation (UBC), or the FDA were not eligible to participate, nor were respondents who participated in the previous waves of the survey (12-month TIRF REMS Access Program Assessment, the 24-month TIRF REMS Access Program Assessment, or the 36-month TIRF REMS Access Program Assessment).

3.1.2 Recruitment

Subjects were recruited via an invitation letter via email and through the United States Postal Service (USPS) (Section 5.1.1 for more detail).

The required number of completed surveys was not achieved within approximately 10 days after the first mailing; thus, additional invitations were sent via email to non-respondents from the original sample to maximize participation.

Each letter of invitation included a unique code needed to access the survey. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed).

Prescribers were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. The survey was estimated to take approximately 20 minutes to complete.

All respondents who completed the survey and provided their contact information were mailed a $125 gift card for participating, with the exception of prescribers who practiced in Massachusetts, Minnesota or Vermont (due to state laws prohibiting it). The mailing also included a copy of the Important Safety Information (ISI) and a copy of the correct answers to key risk message questions.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the prescribers' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that use "True" or "Yes" vs. "False" or "No" response options, the desired response for key risk messages is generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the survey protocol (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the prescriber's knowledge of the specific contraindications for TIRF medicine in opioid non-tolerant patients and under what conditions a patient is considered opioid tolerant.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	***True***
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	***False***
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	***False***
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired response**
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***
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:	
13a	8 mg oral hydromorphone/day	***True***
13b	60 mg oral morphine/day	***True***
13c	30 mg oral oxycodone/day	***True***
13d	25 mcg transdermal fentanyl/hour	***True***
13e	25 mg oral oxymorphone/day	***True***
13f	An equianalgesic dose of another oral opioid	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the prescriber's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients, and the timing of administration of the TIRF medicine in relation to the around-the-clock opioid therapy to ensure the patient is considered opioid tolerant. This key risk message includes a behavior question (Questions 9) and knowledge questions (Questions 6 and 15, and components of Question 20).

Key Risk Message 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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired response**
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
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***
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	***False***
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	Chronic non-cancer pain	***No***
15	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	***15b. 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.***
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.	
20b	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	***True***
20c	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	***False***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the prescriber's knowledge of the risk factors for opioid abuse and importance in monitoring for signs of abuse in patients who take TIRF medicines.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the prescriber's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
12c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
12d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***
16	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. According to the labeling, how should the prescriber proceed? Please select one option.	***16b. The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.***

3.3 Additional Questions

The survey also contained questions (Question 14a-f) about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following questions about behaviors were asked after the key risk message questions.

Question No.	Question
14	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know."
14a	Ask patients (or their caregivers) about the presence of children in the home
14b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
14c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
14d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
14e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
14f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 Primary Analysis Population

The primary population for analysis was all eligible prescribers who completed the survey. Eligible prescribers were defined as those respondents who answered Yes to Question 1 (agree to take part in survey) and Yes to Question 3 (enrolled in the TIRF REMS Access Program), and No to Question 2 (participated in past survey) and No to Question 4 (worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA). A survey was considered "completed" when an eligible prescriber answered all relevant questions.

4.2 Primary Analysis

Primary analyses were performed for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/component included in the key risk message. Confidence intervals (95% CI) were calculated using the exact binomial method around the percentage of correct responses.

Primary analyses were then stratified by questions/characteristics of interest:

1) Those who indicated they both received/had access to and read the Medication Guide and Full Prescribing Information versus those who did not and those who responded they did not or did not know whether they had (Questions 21-24).
2) Medical degree of respondents (Question 33).
3) Whether the survey was completed via the internet or telephone

4) Time practicing medicine (Question 34).

5) The number of times per month they prescribed TIRF medicines within the last 6 months (Question 30).

6) Respondents practicing in a Closed Healthcare System (Question 35).

Stratified analyses were conducted only when at least two of the stratified response categories had at least 50 respondents (e.g., for analysis 3 above, at least 50 prescribers had to respond they completed the survey via the internet and at least 50 had to respond they completed it by telephone in order for that analysis to be conducted).

4.3 Secondary Analysis

As an indicator of the overall level of comprehension of the entire key risk message, descriptive analyses of the number and percentage of responders who answered various proportions of the key risk message components correctly are presented (e.g., the proportion who answered one question in the key risk message correctly, those who answered two questions correctly, those who answered three component questions correctly, etc.). Confidence intervals (95% CI) were calculated for the proportion of respondents who answered all component questions of the key risk message correctly.

4.4 Prescriber Report of a Potential Adverse Event, Product Complaint, or Medical Information Request during the Survey

A prescriber may have reported a potential adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the event or complaint, the verbatim response, and the prescriber's contact information, if provided. The prescriber was also informed that a representative from the appropriate TIRF medicine sponsor might contact him/her to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Adverse Event/Product Complaint Project Specific Procedure (AE/PC PSP).

5. RESULTS

Results of the prescriber's responses to questions in the KAB survey are summarized in this section; stratified analysis tables and overall listings are provided in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 8210 prescribers were sent letters inviting them to participate in this survey (Table 1). An additional 19,215 reminder letters were sent to non-responders (See Section 3.1 for

survey methodology details). Most prescribers received more than 1 reminder letter. Once the target number of completed surveys was achieved (a sample of 300 prescribers was planned), the survey was closed.

As noted in Section 3.1, the survey was expected to be open through 20 October 2015. The survey launch date had been delayed in order to incorporate FDA feedback on the survey received in the 36-Month FDA Assessment Report Acknowledgement Letter. Successful recruitment resulted in the survey closing earlier than expected on 16 October 2015.

From the total of 587 respondents who accessed the survey, 350 prescribers (59.6%) met eligibility criteria, and of those who met eligibility criteria, 310 (88.6%) completed the survey. One respondent completed the survey twice. Only the responses from the first survey were included. Of these 310 prescribers, 303 (97.7%) completed the survey online, and 7 (2.3%) completed it by telephone (Table 3).

Based on the TRIG Sponsors interpretation of state laws regarding prescriber reimbursement, respondents from Massachusetts, Vermont, and Minnesota were eligible to participate in the survey. However, they were not eligible to receive the $125 honorarium. Four respondents from Massachusetts and two respondents from Minnesota participated in the survey.

Table 1. Survey Participant Administration Results

Summary Statistic	N	%
Number of invitations distributed	8210	
Number of invitations returned as undeliverable	437	
Number of reminder letters distributed	19,215	
All Respondents [1]	587	7.6
Eligible Respondents [2]	350	59.6
Completed survey [3]	310	88.6
Did not complete the survey [3]	40	11.4
Respondents not eligible [2,4]	237	40.4

[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentages are based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

As shown in Table 2, of the 587 prescribers who accessed the survey, 489 prescribers answered at least 1 survey question and 98 respondents did not answer any of the survey

questions and were discontinued. Of the 489 prescribers who started the survey, 485 agreed to participate. During the screening process it was determined that 139 of the 489 respondents who answered at least 1 survey question were not eligible to participate in the survey because they either did not agree to participate in the survey (4 respondents), indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before (86 respondents), were not enrolled or did not know whether they were enrolled in the TIRF REMS Access Program (31 respondents), or indicated they, or an immediate family member, had worked for a TRIG company, UBC, or FDA in the past or did not know if they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past (16 respondents). In addition, 2 of the 489 prescribers who answered at least 1 survey question discontinued the survey at Question 3. Thus, there were 350 eligible participants (Table 2), with 310 (88.6%) completing the survey (Table 1).

Table 2. Survey Participant Screening Results

Question	Screened Prescribers N=587	
	n	%
Question 1: Do you agree to take part in this survey?		
Yes	485	82.6
No [1]	4	0.7
Discontinued	98	16.7
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.		
Yes [1]	30	5.1
No	399	68.0
I don't know [1]	56	9.5
Question not asked [2]	4	0.7
Discontinued	98	16.7

Table 2. Survey Participant Screening Results

Question	Screened Prescribers N=587	
	n	%
Question 3: Are you enrolled in the TIRF REMS Access Program?		
Yes	366	62.4
No [1]	17	2.9
I don't know [1]	14	2.4
Question not asked [2]	90	15.3
Discontinued	100	17.0
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply. [3]		
Actavis Laboratories FL, Inc [1]	1	0.2
Anesta LLC [1]	0	
BioDelivery Services International, Inc. (BDSI) [1]	0	
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) [1]	3	0.5
Depomed, Inc. [1]	0	
Galena Biopharma, Inc. [1]	0	
Insys Therapeutics, Inc. [1]	5	0.9
Mallinckrodt Pharmaceuticals [1]	0	
McKesson Specialty Care Solutions [1]	0	
Mylan, Inc. [1]	0	
Par Pharmaceutical, Inc. [1]	0	
RelayHealth [1]	0	
Teva Pharmaceuticals, Ltd. [1]	2	0.3
United BioSource Corporation [1]	0	
FDA [1]	0	
None of these apply [4]	350	59.6
I don't know [1]	3	0.5

Table 2. Survey Participant Screening Results

Question	Screened Prescribers N=587	
	n	%
Prefer not to answer [1]	3	0.5
Question not asked [1]	121	20.6
Discontinued	100	17.0

[1] Ineligible to participate in the survey.

[2] Question not asked due to previous question termination.

[3] More than one response can be selected, so percentages may not sum to 100%.

[4] Ineligible to participate in the survey if selected additionally to another response.

Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

Prescribers taking the survey online took a mean of 16 minutes to complete it, while those taking it by telephone took a mean of 25 minutes (Table 3).

Table 3. Time to Complete Survey for Completers Only

Time to Complete Survey (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total [1]**
N	7	303	310
Mean (± SD)	25.37 (4.816)	16.33 (7.797)	16.54 (7.853)
Minimum	20.1	4.0	4.0
Median	25.05	15.00	15.10
Maximum	35.3	60.4	60.4
Category			
0 to <5 Minutes	0	1	1
5 – <10 Minutes	0	59	59
10 – <15 Minutes	0	91	91
15 – <20 Minutes	0	85	85

Table 3. Time to Complete Survey for Completers Only

Time to Complete Survey (Minutes)			
Summary Statistic	**Telephone**	**Internet**	**Total [1]**
20 – <25 Minutes	3	37	40
25 – <30 Minutes	3	12	15
30 Minutes or More	1	18	19

[1] Number of eligible prescribers completing the survey (See Table 1).

5.1.2 Description of Eligible Prescribers who Completed the Survey

The demographic characteristics of prescribers who completed the survey are shown in Table 4.

The majority of respondents are male (61.9%) and most respondents (95.5%) did not practice within a closed healthcare system (question added as requested by the FDA). Most respondents had prescribed a TIRF medicine either not at all (24.8%) or 1-2 times per month (49.7%) within the 6 months preceding the survey, and of the TIRF medicines prescribed within the last 6 months, Actiq® or generic Actiq® was most frequently prescribed (58.8%).

The most common healthcare degree among respondents was MD (57.4%), and the most common medical specialty was pain management (48.7%). Most prescribers had practiced medicine for 6 years or longer (73.9%).

The survey included 31.3% of respondents from the South, 30.6% from the West, 22.6% from the Northeast, and 14.8% from the Midwest region of the United States (US). There was 1 respondent from Puerto Rico identified as "Other" in Table 4.

Table 4. Description of Eligible Prescribers

Question	Eligible/Completed Prescribers N=310 [1]	
	n	**%**
Question 30: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?		
None	77	24.8
1 – 2 times per month	154	49.7
3 – 5 times per month	49	15.8
More than 5 times per month	17	5.5
I don't remember	13	4.2

Table 4. Description of Eligible Prescribers

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 31: Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply. [2]		
Abstral®	26	11.2
Actiq ® or generic Actiq®	137	58.8
Fentora ®	94	40.3
Lazanda ®	22	9.4
Subsys ®	105	45.1
N/A (answered ***None*** to Question 30)	77	
Question 32: What is your gender?		
Male	192	61.9
Female	116	37.4
Prefer not to answer	2	0.6
Question 33: What is your medical degree?		
MD	178	57.4
DO	26	8.4
Nurse Practitioner	68	21.9
Physician Assistant	35	11.3
Prefer not to answer	3	1.0
Question 34: In total, how many years have you been practicing medicine, since completing your post-graduate education?		
Less than 3 years	41	13.2
3-5 years	38	12.3
6-10 years	71	22.9
11-15 years	51	16.5
More than 15 years	107	34.5
Prefer not to answer	2	0.6

Table 4. Description of Eligible Prescribers

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 35: Do you practice in a closed healthcare system, such as: (b) (4) VA, DoD, or NIH?		
Yes	14	4.5
No	296	95.5
Question 36: In which state or US territory do you practice? [3]		
Northeast	70	22.6
Midwest	46	14.8
South	97	31.3
West	95	30.6
Other	1	0.3
Prefer not to answer	1	0.3
Question 37: What is your medical specialty?		
Oncology	65	21.0
Primary Care	28	9.0
Pain Management	151	48.7
Other (please specify) [4]	65	21.0
No designated specialty	1	0.3

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.
[4] Verbatim text for question about medical specialty are presented in Appendix B, Listing 4.

5.1.2.1 Comparison of Survey Respondents to the General Population of Prescribers

Comparison of the survey respondents to the general population of TIRF prescribers (as requested by the FDA) showed the geographic distribution of respondents to the prescriber survey was similar to the overall population of prescribers who prescribe TIRF medicines (Table 5).

Table 5. Comparison of Survey Respondents to General Population of TIRF Prescribers

Question	Eligible/Completed Prescribers (N=310) n (%)	Prescribers of TIRF Medicines in the Past 6 Months [1] (N=8812) n (%)
Geographic Distribution [2]		
Northeast	70 (22.6)	1854 (21.0)
Midwest	46 (14.8)	1532 (17.4)
South	97 (31.3)	3047 (34.6)
West	95 (30.6)	2374 (26.9)
Other	1 (0.3)	5 (0.1)
Prefer not to answer	1 (0.3)	0

[1] Based on data obtained from the TIRF REMS Access Program database.

[2] Based on Prescriber KAB Survey Question 36; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Note: Percentages are based on the prescribers with informative data.

5.1.3 TIRF Medicines Educational Materials

Prescribers were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information, the Medication Guide, and the Patient-Prescriber Agreement Form (PPAF) (Table 6). Almost all prescribers reported they had received or had access to the Full Prescribing Information (92.3%) and the Medication Guide (89.0%). Of those with access to these materials, 83.2% indicated that they had read the Full Prescribing Information and 93.1% indicated that they had read the Medication Guide. Additionally, most prescribers reported reviewing the PPAF with each patient or their caregiver (92.3%); and of those, 93.0% indicated they and the patient/caregiver sign the PPAF and 87.1% indicated that they give a copy of the PPAF to the patient or the patient's caregiver.

Table 6. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 21: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?		
Yes	286	92.3
No	9	2.9
I don't know	15	4.8
Question 22: Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe? [2]		
Yes	238	83.2
No	41	14.3
I don't know	7	2.4
N/A (answered ***No*** or ***I don't know*** to Question 21)	24	
Question 23: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?		
Yes	276	89.0
No	10	3.2
I don't know	24	7.7
Question 24: Did you read the Medication Guide for the TIRF medicine(s) that you prescribe? [2]		
Yes	257	93.1
No	14	5.1
I don't know	5	1.8
N/A (answered ***No*** or ***I don't know*** to Question 23)	34	
Question 25: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?		
Yes [3]	12	3.9
No	272	87.7
I don't know	26	8.4

Table 6. Responses to Questions About the TIRF Medicines Educational Materials and the TIRF Patient-Prescriber-Agreement Form

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 27: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?		
Yes	286	92.3
No	17	5.5
I don't know	7	2.3
Question 28: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her? [2]		
Yes	266	93.0
No	9	3.1
I don't know	11	3.8
N/A (answered ***No*** or ***I don't know*** to Question 27)	24	
Question 29: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver? [2]		
Yes	249	87.1
No	21	7.3
I don't know	16 (5.6)	5.6
N/A (answered ***No*** or ***I don't know*** to Question 27)	24	

[1] Number of eligible prescribers completing the survey (See Table 1)
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[3] Verbatim text for questions about the information in the Full Prescribing Information or Medication Guide is presented in Appendix B, Listing 3.

5.2 Key Risk Messages

5.2.1 Key Risk Message 1

Key Risk Message 1 refers to the prescriber's knowledge of the specific contraindications for TIRF medicine in opioid non-tolerant patients and under what conditions a patient is considered opioid tolerant.

Most prescribers knew that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer

(95.2%, 95% CI: 92.1-97.3) and are those who are currently taking opioid therapy (93.9%, 95% CI: 90.6-96.3) (Table 7). In addition, most understood that cancer patients with no known contraindications to the drug fentanyl, but who are not taking around-the-clock opioid therapy, are not considered opioid tolerant (86.8%, 95% CI: 82.5-90.3).

Ninety percent (90.3%, 95% CI: 86.5-93.4) of prescribers knew that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (96.1%, 95% CI: 93.3-98.0). Eighty-five percent (84.8%, 95% CI: 80.4-88.6) were aware that TIRF medicines may not be used to treat opioid non-tolerant patients. Similarly, 85.5% (95% CI: 81.1-89.2) of prescribers were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product.

The majority of prescribers were aware of the regimens that defined an opioid-tolerant patient: 8 mg oral hydromorphone/day (72.9%, 95% CI: 67.6-77.8), 60 mg oral morphine/day (94.5%, 95% CI:91.4-96.8), 30 mg oral oxycodone/day (78.7%, 95% CI: 73.7-83.1), 25 mcg transdermal fentanyl/hour (85.5%; 95% CI: 81.1-89.2), 25 mg oral oxymorphone/day (72.3%, 95% CI: 66.9-77.2), and an equianalgesic dose of another oral opioid (67.7%, 95% CI: 62.2-72.9).

Overall, 30.3% (95% CI: 25.3-35.8) of respondents answered all 13 components of key risk message 1 correctly, 52.6% missed no more than one component and 67.8% missed no more than two.

Analyses stratified by whether the Full Prescribing Information and Medication Guide were received and read (Received and read: N=273; Did not receive or read: N=37), by modality for completing the survey (internet [N=303] versus telephone [N=7]) and whether the prescribers practiced in a closed healthcare system (Yes: N=14; No: N=296) were not performed for any of the key risk messages because they did not meet the criteria of ≥50 respondents within at least two response categories.

No trends were evident when the results for key risk message 1 were stratified by the healthcare degree of respondents, time practicing medicine, or number of times TIRF medicines were prescribed in the past 6 months (Appendix B).

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Prescribers N=310[1]	
	n	% (95% CI)[2]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer		
True [3]	295	95.2 (92.1 - 97.3)
False	14	4.5
I don't know	1	0.3
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	15	4.8
False [3]	291	93.9 (90.6 - 96.3)
I don't know	4	1.3
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	33	10.6
False [3]	269	86.8 (82.5 - 90.3)
I don't know	8	2.6
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True [3]	280	90.3 (86.5 - 93.4)
False	23	7.4
I don't know	7	2.3
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True [3]	298	96.1

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Prescribers N=310[1]	
	n	% (95% CI)[2]
		(93.3 - 98.0)
False	2	0.6
I don't know	10	3.2
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		
True	38	12.3
False [3]	263	84.8 (80.4 - 88.6)
I don't know	9	2.9
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True [3]	265	85.5 (81.1 - 89.2)
False	40	12.9
I don't know	5	1.6
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:		
13a: 8 mg oral hydromorphone/day		
True [3]	226	72.9 (67.6 - 77.8)
False	57	18.4
I don't know	27	8.7
13b: 60 mg oral morphine/day.		
True [3]	293	94.5 (91.4 - 96.8)
False	11	3.5
I don't know	6	1.9

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Prescribers N=310[1]	
	n	% (95% CI)[2]
13c: 30 mg oral oxycodone/day		
True [3]	244	78.7 (73.7 - 83.1)
False	46	14.8
I don't know	20	6.5
13d: 25 mcg transdermal fentanyl/hour		
True [3]	265	85.5 (81.1 - 89.2)
False	27	8.7
I don't know	18	5.8
13e: 25 mg oral oxymorphone/day		
True [3]	224	72.3 (66.9 - 77.2)
False	33	10.6
I don't know	53	17.1
13f: An equianalgesic dose of another oral opioid		
True [3]	210	67.7 (62.2 - 72.9)
False	55	17.7
I don't know	45	14.5
Secondary Analysis: Number of Correct Responses		
0 correct responses	0	
1 correct response	0	
2 correct responses	1	0.3
3 correct responses	1	0.3
4 correct responses	1	0.3

Table 7. Responses Linked to Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients

Question	Eligible/Completed Prescribers N=310[1]	
	n	% (95% CI)[2]
5 correct responses	0	
6 correct responses	7	2.3
7 correct responses	10	3.2
8 correct responses	21	6.8
9 correct responses	23	7.4
10 correct responses	36	11.6
11 correct responses	47	15.2
12 correct responses	69	22.3
13 correct responses	94	30.3 (25.3 - 35.8)

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

[3] Indicates the correct response(s) to each question or component within a question.

5.2.2 Key Risk Message 2

Key Risk Message 2 refers to the prescriber's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients, and the timing of administration of the TIRF medicine in relation to the around-the-clock opioid therapy to ensure the patient is considered opioid tolerant.

Sixty-nine percent (69.0%, 95% CI: 63.6-74.1) of prescribers correctly indicated that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time, and 72.9% (95% CI: 67.6-77.8) correctly indicated that a cancer patient who had been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain (Table 8).

In addition, 92.9% of prescribers (95% CI: 89.5-95.5) were aware that TIRF medicines are indicated for opioid-tolerant patients with breakthrough pain from cancer and not for patients with acute or postoperative pain (90.3%, 95% CI: 86.5-93.4), headache or migraine pain (94.8%, 95% CI: 91.8-97.0), or dental pain (98.4%, 95% CI: 96.3-99.5). Sixty-five percent (64.8%, 95% CI: 59.2-70.2) correctly responded that TIRF medicines should not be prescribed for chronic non-cancer pain. The 34.2% of prescribers who stated they do

prescribe TIRF medicines for chronic non-cancer pain were presented with 2 additional questions as requested by FDA. Question 10 addressed the type of chronic pain conditions they prescribe a TIRF medicine to treat (Table 9). The most frequently reported conditions were back pain (32.1%), cancer pain (22.6%), neuropathic pain (21.7%), post-operative pain (18.9%), and chronic pain (17.9%). Question 11 addressed the reasons for selecting a TIRF medicine to treat these conditions (Table 10). The most frequently reported reasons were efficacy (35.8%), that they are fast acting (34.0%), and that other types of medications have failed (28.3%). Verbatim responses for Questions 10 and 11 can be found in Listing 1.1 and Listing 2.1, respectively (Appendix B).

Most prescribers (73.2%, 95% CI: 67.9-78.1) correctly indicated that a TIRF medicine should not be prescribed to an adult female with localized breast cancer who just completed a mastectomy and reconstructive surgery and who has persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks (Table 8).

A high percentage of prescribers (93.9%, 95% CI: 90.6-96.3) were aware that patients must be informed that TIRF medicines should not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain; and most (72.9%, 95% CI: 67.6-77.8) correctly indicated that patients should be instructed that if they stop taking their around-the-clock opioid medicine, they cannot continue to take their TIRF medicine.

Overall, 26.5% (95% CI: 21.6-31.7) correctly answered all components of the key risk message, 53.0% missed no more than one component question, and 71.4% missed no more than two of the 10 component questions.

Table 8. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	75	24.2
False [3]	214	69.0 (63.6 - 74.1)
I don't know	21	6.8

Table 8. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
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.		
True	62	20.0
False [3]	226	72.9 (67.6 - 77.8)
I don't know	22	7.1
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	28	9.0
No [3]	280	90.3 (86.5 - 93.4)
I don't know	2	0.6
9b: Headache or migraine pain		
Yes	16	5.2
No [3]	294	94.8 (91.8 - 97.0)
I don't know	0	
9c: Dental pain		
Yes	5	1.6
No [3]	305	98.4 (96.3 - 99.5)
I don't know	0	
9d: Breakthrough pain from cancer		
Yes [3]	288	92.9 (89.5 - 95.5)

Table 8. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
No	22	7.1
I don't know	0	
9e: Chronic non-cancer pain		
Yes	106	34.2
No [3]	201	64.8 (59.2 - 70.2)
I don't know	3	(1.0)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
15a: Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	26	8.4
15b: 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. [3]	227	73.2 (67.9 - 78.1)
15c: 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.	18	5.8
15d: Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	19	6.1
15e: I don't know	20	6.5

Table 8. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
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.		
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain**.**		
True [3]	291	93.9 (90.6 - 96.3)
False	12	3.9
I don't know	7	2.3
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.		
True	64	20.6
False [3]	226	72.9 (67.6 - 77.8)
I don't know	20	6.5
Secondary Analysis: Number of Correct Responses		
0 correct response	0	
1 correct response	0	
2 correct responses	1	0.3
3 correct responses	3	1.0
4 correct responses	5	1.6
5 correct responses	12	3.9
6 correct responses	29	9.4
7 correct responses	39	12.6
8 correct responses	57	18.4

Table 8. Responses Linked to Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-The-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
9 correct responses	82	26.5
10 correct responses	82	26.5 (21.6 - 31.7)

[1] Number of eligible prescribers completing the survey (See Table 1)

[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

[3] Indicates the correct response(s) to each question or component within a question.

Table 9. Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106) [1] n (%)	
	n	%
Question 10: For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?		
Total Number of Responses [2]	214	
Back Pain	34	32.1
Cancer Pain	24	22.6
Neuropathic Pain	23	21.7
Post-operative Pain	20	18.9
Chronic Pain	19	17.9
Joint Pain	11	10.4
Reflex Sympathetic Dystrophy	10	9.4
Complex Regional Pain Syndrome	8	7.5
Spinal Pain	8	7.5

Table 9. Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106) [1] n (%)	
	n	%
Neck Pain	5	4.7
Abdominal Pain	4	3.8
Musculoskeletal Pain	4	3.8
Sickle Cell	4	3.8
Gastrointestinal Pain	3	2.8
Migraines	3	2.8
Palliative Care	3	2.8
Pancreatitis	3	2.8
Spinal Stenosis	3	2.8
Breakthrough Pain	2	1.9
Oral Pain	2	1.9
Wound Pain	2	1.9
Allergic to Morphine and Dilaudid	1	0.9
Chronic Wounds	1	0.9
Intestinal Absorption Problems	1	0.9
Ischemic Peripheral Vascular Disease	1	0.9
Multiple Sclerosis	1	0.9
Neuropathy	1	0.9
Radiculopathy	1	0.9
Somatic Pain	1	0.9

Table 9. Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106) [1] n (%)	
	n	%
Trauma Pain	1	0.9
Wound Care	1	0.9
Other[3]	9	8.5

[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Chronic Non-Cancer Pain-"Yes"*) and were subsequently presented Question 10 and Question 11.

[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.

[3] Other includes responses that were not categorized or responses that did not include a medical condition (see Appendix B Listing 1.1).

Table 10. Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106) [1]	
	n	%
Question 11: Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?		
Total Number of Responses [2]	169	
Efficacy	38	35.8
Fast Acting	36	34.0
Other Types of Medications have Failed	30	28.3
Breakthrough Pain	15	14.2
Ease of Use	5	4.7
Preferred Route of Administration	5	4.7
Abuse/Diversion Deterrence	4	3.8

Table 10. Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106) [1]	
	n	%
Long Duration of Action	4	3.8
Opioid Rotation	3	2.8
Potency	3	2.8
Quality of Life	3	2.8
Insurance	2	1.9
Pain Management	2	1.9
Compliance	1	0.9
Consistent Control	1	0.9
Less Toxicities Compared to Other Opioids	1	0.9
Patient Cannot Tolerate Other Options	1	0.9
Practice Preference	1	0.9
Preferred route of Administration	1	0.9
Prescribed by Another Physician before Becoming a Patient	1	0.9
Severe Pain	1	0.9
Other [3]	11	10.4

[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Chronic Non-Cancer Pain-"Yes"*) and were subsequently presented Question 10 and Question 11.

[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.

[3] Other includes responses that were not categorized or responses that did not include a medical condition (see Appendix B Listing 2.1).

Stratification by number of times TIRF medicines were dispensed in the last 6 months resulted in one numeric trend (not statistically significant; Table 11). The more frequently TIRF medicines were prescribed within the past 6 months, the more likely prescribers were to prescribe them for dental pain. No other trends were observed (Appendix B).

Table 11. Key Risk Message 2: Trends in Correct Response Rates by Prescribing Frequency Within Last 6 Months

Question	Stratification Question									
	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months									
	None (N=77)		1 - 2 times per month (N=154)		3 - 5 times per month (N=49)		More than 5 times per month (N=17)		I don't remember (N=13)	
	Correct Response Rate		Correct Response Rate		Correct Response Rate		Correct Response Rate		Correct Response Rate	
	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]	n	% (95% CI) [1]
Key Risk Message 2										
9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.										
9c. Dental pain										
No	77	100.0 (95.3-100.0)	153	99.4 (96.4-100.0)	47	95.9 (86.0 - 99.5)	15	88.2 (63.6 - 98.5)	13	100.0 (75.3-100.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

5.2.3 Key Risk Message 3

Key Risk Message 3 refers to the prescriber's knowledge of the risk factors for opioid abuse and importance of monitoring for signs of abuse in patients who take TIRF medicines.

Results in Table 12 show that 98.7% (95% CI: 96.7-99.6) of prescribers were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines. In addition, most respondents correctly indicated that a personal history of psychiatric illness is a risk factor for opioid abuse (84.5%, 95% CI: 80.0-88.4), that a personal history of past or current alcohol or drug abuse or family history of drug or alcohol abuse is a risk factor for opioid abuse (98.7%, 95% CI: 96.7-99.6); and that TIRF medicines can be abused in a manner similar to other opioid agonists (94.2%, 95% CI: 91.0-96.5).

Overall, 79.0% (95% CI: 74.1-83.4) of prescribers correctly answered all components of the key risk message, and 97.7% missed no more than one of the 4 component questions.

Stratification by degree, time in practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any evident trends (Appendix B).

Table 12. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics

Question	Eligible/Completed Prescribers N= 310 [1]	
	n	% (95% CI) [2]
Question 7: Please answer True, False, or I don't know for each statement about TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True [3]	306	98.7 (96.7 - 99.6)
False	2	0.6
I don't know	2	0.6
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes [3]	262	84.5 (80.0 - 88.4)
No	28	9.0
I don't know	20	6.5

Table 12. Responses Linked to Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist, and a Schedule II Controlled Substance, With Abuse Liability Similar to Other Opioid Analgesics

Question	Eligible/Completed Prescribers N= 310 [1]	
	n	% (95% CI) [2]
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes [3]	306	98.7 (96.7 - 99.6)
No	4	1.3
I don't know	0	
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True [3]	292	94.2 (91.0 - 96.5)
False	12	3.9
I don't know	6	1.9
Secondary Analysis: Number of Correct Responses		
0 correct responses	1	0.3
1 correct response	0	
2 correct responses	6	1.9
3 correct responses	58	18.7
4 correct responses	245	79.0 (74.1 - 83.4)

[1] Number of eligible prescribers completing the survey (See Table 1)
[2] All confidence intervals are exact binomial 95% confidence intervals.
[3] Indicates the correct response(s) to each question or component within a question.

5.2.4 Key Risk Message 4

Key Risk Message 4 refers to the prescriber's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Almost all prescribers (92.6%; 95% CI: 89.1-95.2) understood TIRF medicines are not interchangeable with each other regardless of the route of administration; 95.5% (95% CI:

92.5-97.5) understood the conversion of one TIRF medicine to another may result in a fatal overdose; and 90.0% (95% CI: 86.1-93.1) understood that dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (Table 13). The majority of prescribers (77.4%, 95% CI: 72.4-82.0) correctly indicated that, when a patient wants to change his/her TIRF medicine, the prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

Overall, 67.7% (95% CI: 62.2-72.9) of prescribers correctly answered all components of the key risk message, 92.2% missed no more than one of the 4 component questions.

Stratification by degree, time in practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any evident trends (Appendix B).

Table 13. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
Question 12: Please answer True, False, or I don't know for each statement about TIRF medicines.		
12b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	13	4.2
False [3]	287	92.6 (89.1 - 95.2)
I don't know	10	3.2
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True [3]	296	95.5 (92.5 - 97.5)
False	6	1.9
I don't know	8	2.6
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True [3]	279	90.0 (86.1 - 93.1)
False	21	6.8
I don't know	10	3.2

Table 13. Responses Linked to Key Risk Message 4: TIRF Medicines Are Not Interchangeable With Each Other, Regardless of Route of Administration

Question	Eligible/Completed Prescribers N=310 [1]	
	n	% (95% CI) [2]
16: 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. According to the labeling, how should the prescriber proceed? Please select one option.		
16a: The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	3	1.0
16b: The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose. [3]	240	77.4 (72.4 - 82.0)
16c: Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	22	7.1
16d: 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.	33	10.6
16e: I don't know	12	3.9
Secondary Analysis: Number of Correct Responses		
0 correct responses	3	1.0
1 correct response	8	2.6
2 correct responses	13	4.2
3 correct responses	76	24.5
4 correct responses	210	67.7 (62.2 - 72.9)

[1] Number of eligible prescribers completing the survey (See Table 1).

[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

[3] Indicates the correct response(s) to each question or component within a question.

5.2.5 Other Survey Questions

5.2.5.1 Additional Questions about TIRF Medicines Safety

Table 14 summarizes the prescribers' responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages.

A high percentage of prescribers (90.6%) correctly indicated a family history of asthma is not a risk factor for opioid abuse.

Most prescribers (86.1%) correctly indicated that for a patient starting a TIRF medicine, an appropriate dose is the lowest available dose, unless the Full Prescribing Information provides specific guidance. When presented with the scenario of a patient who has started on the lowest dose of a TIRF medicine, and for whom the breakthrough pain has not been sufficiently relieved after 30 minutes, 68.7% prescribers correctly responded that they should follow the guidance based on the product-specific Medication Guide because the recommendations are not the same for all TIRF medicines.

The majority of prescribers (75.8%) correctly indicated use of a TIRF medicine with a CYP3A4 inhibitor may require a dose adjustment, and that the patient needs to be monitored for opioid toxicity to minimize the risk of fatal respiratory depression.

Nearly all prescribers surveyed (99.4%) understood that TIRF medicines contain fentanyl in an amount that could be fatal for children of all ages, for individuals for whom they were not prescribed, and for those who are not opioid tolerant. In addition, 99.7% understood that patients must be instructed not to share their TIRF medicine with anyone else, even if that person has the same symptoms.

Table 14. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8c: A family history of asthma		
Yes	12	3.9
No [2]	281	90.6
I don't know	17	5.5

Table 14. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 17: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.		
17a. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	35	11.3
17b. The dose that the prescriber believes is appropriate based on their clinical experience.	3	1.0
17c. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance. [2]	267	86.1
17d. The median available dose.	2	0.6
17e. I don't know.	3	1.0
Question 18: 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? Please pick the best option of the scenarios described.		
18a. Take another (identical) dose of the TIRF medicine immediately.	78	25.2
18b. Take a dose of an alternative rescue medicine.	13	4.2
18c. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines. [2]	213	68.7
18d. Double the dose and take immediately.	5	1.6
18e. I don't know.	1	0.3
Question 19: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.		
19a: The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	14	4.5
19b: 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. [2]	235	75.8
19c: There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	6	1.9
19d: The dose of the TIRF medicine must be reduced by one-half if a CYP3A4 inhibitor is prescribed in the same patient.	10	3.2

Table 14. Responses to Additional Questions About the Safe Use of TIRF Medicines

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
19e: I don't know.	45	14.5
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.		
20a: 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.		
True [2]	308	99.4
False	1	0.3
I don't know	1	0.3
20d: Instruct patients never to share their TIRF medicine with anyone else, even if that person has the same symptoms.		
True [2]	309	99.7
False	0	
I don't know	1	0.3

[1] Number of eligible prescribers completing the survey (See Table 1).
[2] Indicates the correct response(s) to each question or component within a question.

5.2.5.2 Prescriber Activities When Prescribing TIRF Medicines

Prescribers were asked about specific activities performed when prescribing TIRF medicines (Table 15).

More than half of prescribers indicated they always ask patients (or their caregivers) about the presence of children in the home (57.4%), always instruct patients (or their caregivers) not to share TIRF medicines with anyone else (80.3%), always counsel patients (or their caregivers) that accidental exposure by a child may be fatal (65.5%), always instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children (71.0%), and always instruct patients (or their caregivers) about proper disposal of TIRF medicines (61.3%).

In addition, 45.2% indicated they always give patients (or their caregivers) the Medication Guide for their TIRF medicine, whereas 39.7% indicated they give it only with the first prescription.

Table 15. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
Question 14: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.		
14a: Ask patients (or their caregivers) about the presence of children in the home.		
Always	178	57.4
Only with the first prescription	75	24.2
Sometimes	42	13.5
Never	11	3.5
I don't know	4	1.3
14b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else.		
Always	249	80.3
Only with the first prescription	43	13.9
Sometimes	13	4.2
Never	3	1.0
I don't know	2	0.6
14c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal.		
Always	203	65.5
Only with the first prescription	66	21.3
Sometimes	27	8.7
Never	11	3.5
I don't know	3	1.0

Table 15. Responses to All Questions About Activities When Prescribing TIRF Medicines

Question	Eligible/Completed Prescribers N=310 [1]	
	n	%
14d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure.		
Always	220	71.0
Only with the first prescription	61	19.7
Sometimes	19	6.1
Never	7	2.3
I don't know	3	1.0
14e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines.		
Always	190	61.3
Only with the first prescription	74	23.9
Sometimes	37	11.9
Never	6	1.9
I don't know	3	1.0
14f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine.		
Always	140	45.2
Only with the first prescription	123	39.7
Sometimes	23	7.4
Never	21	6.8
I don't know	3	1.0

[1] Number of eligible prescribers completing the survey (See Table 1).

5.3 Spontaneous Reporting of Adverse Events, Product Complaints or Medical Information Requests

Among all survey respondents (N=310, Table 1), there were 86 reports of a potential adverse event or product complaint associated with the use of TIRF medicines made within the survey free text field during the online survey, and 4 reports made during the telephone survey. Verbatim statements are provided in Appendix B, Listing 5.

6. DISCUSSION AND CONCLUSIONS

Discussion

Survey invitations (and reminders) were sent to a random sample of prescribers enrolled in the TIRF REMS Access Program. From among those who responded to the invitation, 310 prescribers completed the survey. Thus, the required sample size was achieved within the planned survey period.

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed.

Comparison of survey respondents to the general population of TIRF prescribers (as requested by FDA) showed the geographic distribution of respondents to the prescriber survey was similar to the overall population of prescribers who prescribe TIRF medicines Table 5). A full comparison of demographics of the survey respondents to the general population of TIRF prescribers will be included in the Supplemental Report estimated to be delivered on May 4, 2016.

Of the 31 components included as part of key risk messages, 21 components of the key risk messages had a correct response rate >80% and 9 components had a correct response rate between 67.7% and 78.7%.

For Component 9e, 201 prescribers (64.8%) indicated they do not prescribe TIRF medicines for chronic non-cancer pain. A total of 106 prescribers (34.2%) indicated they do prescribe TIRF medicines for chronic non-cancer pain. The 106 prescribers who indicated they do prescribe TIRF medicines for chronic non-cancer pain were presented with 2 additional questions as requested by the FDA. Question 10 addressed the type of chronic pain conditions they prescribe a TIRF medicine to treat (see Table 9). The most frequently reported conditions were back pain (32.1%), cancer pain (22.6%), neuropathic pain (21.7%), post-operative pain (18.9%), and chronic pain (17.9%). Question 11 addressed the reasons for selecting a TIRF medicine to treat these conditions (see Table 10). The most frequently reported reasons were efficacy (35.8%), that they are fast acting (34.0%), and that other types of medications have failed (28.3%). Given these reasons, and the high percentage of respondents who indicated they received and read the REMS educational materials, the responses to Questions 10 and 11 may reflect behavior more than knowledge. That is, prescribers are aware of the labeled indication but choose to prescribe off-label for certain patients. Component 9e in this survey has had a low correct response rate across all prescriber KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). However, the correct response rate is trending up (Table 16).

There is a clear and consistent indication of improvement (i.e., numeric trend) in knowledge and understanding of the key risk messages. Table 16 includes key risk messages and

questions/components within each key risk message as presented in the 48-month survey. It is important to note the question/component numbering, wording, and association with a specific key risk message may have changed across survey waves based on FDA feedback or other decisions made by the TRIG.

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients					
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: [1]				
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (*Correct Response True*) [1]	7.9[2]	90.4 (86.5, 93.5)	90.0 (86.0, 93.2)	95.2 (92.1 - 97.3)
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response False*)	88.7[2]	88.1 (83.9, 91.5)	87.0 (82.7, 90.6)	93.9 (90.6 - 96.3)
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response False*) [1]	15.6[2]	82.1 (77.3, 86.3)	86.3 (81.9, 90.0)	86.8 (82.5 - 90.3)
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response True*)	87.4 (83.1, 90.9)	87.7 (83.5, 91.2)	86.7 (82.3, 90.3)	90.3 (86.5 - 93.4)

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response True*)	95.7 95.7 (92.8, 97.7)	93.7 (90.3, 96.2)	95.7 (92.7, 97.7)	96.1 (93.3 - 98.0)
7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response False*)	82.5 82.5 (77.7, 86.6)	80.1 (75.2, 84.5)	82.0 (77.2, 86.2)	84.8 (80.4 - 88.6)
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response True*)	83.1 83.1 (78.4, 87.2)	80.8 (75.9, 85.1)	84.0 (79.4, 88.0)	85.5 (81.1 - 89.2)
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:				
13a	8 mg oral hydromorphone/day (*Correct Response True*)	N/A	68.5[2]	70.3[2]	72.9 (67.6 - 77.8)
13b	60 mg oral morphine/day (*Correct Response True*)	N/A	89.1[2]	92.3[2]	94.5 (91.4 - 96.8)
13c	30 mg oral oxycodone/day (*Correct Response True*)	N/A	76.2[2]	78.0[2]	78.7 (73.7 - 83.1)

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
13d	25 mcg transdermal fentanyl/hour (*Correct Response True*)	N/A	80.8[2]	83.7[2]	85.5 (81.1 - 89.2)
13e	25 mg oral oxymorphone/day (*Correct Response True*)	N/A	69.9[2]	74.7[2]	72.3 (66.9 - 77.2)
13f	An equianalgesic dose of another oral opioid (*Correct Response True*)	N/A	65.9[2]	59.0[2]	67.7 (62.2 - 72.9)
Key Risk Message 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® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-the-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain					
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time (*Correct Response False*) [1]	N/A	60.6[2]	60.0[2]	69.0 (63.6 - 74.1)
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 (*Correct Response False*) [1]	N/A	64.9[2]	70.3[2]	72.9 (67.6 - 77.8)

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option. [1]				
9a	Acute or postoperative pain (*Desired Behavior response No*)	86.4 (82.0, 90.1)	93.0 (89.6, 95.6)	87.3 (83.0, 90.9)	90.3 (86.5 - 93.4)
9b	Headache or migraine pain (*Desired Behavior response No*)	86.8 86.8 (82.4, 90.4)	92.4 (88.8, 95.1)	89.7 (85.7, 92.9)	94.8 (91.8 - 97.0)
9c	Dental pain (Desired Behavior response No)	96.0 (93.2, 97.9)	96.7 (94.0, 98.4)	97.3 (94.8, 98.8)	98.4 (96.3 - 99.5)
9d	Breakthrough pain from cancer (*Desired Behavior response Yes*)	95.4 (92.3, 97.4)	92.4 (88.8, 95.1)	96.0 (93.1, 97.9)	92.9 (89.5 - 95.5)
9e	Chronic non-cancer pain (*Desired Behavior Response: No*)	54.3[2]	58.9 (53.2, 64.5)	62.0 (56.2, 67.5)	64.8 (59.2 - 70.2)
15	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? [1]				

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
15b	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 (*Correct Response*)	54.3[2]	65.9[2]	66.3 (60.7, 71.7)	73.2 (67.9 - 78.1)
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.				
20b	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain (*Correct Response True*)	91.7[2]	92.1[2]	90.7[2]	93.9 (90.6 - 96.3)
20c	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine (*Correct Response False*) [1]	68.5[2]	57.9[2]	61.0[2]	72.9 (67.6 - 77.8)

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, with Abuse Liability Similar to other Opioid Analgesics					
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True*)	99.7 (98.2, 100.0)	99.0 (97.1, 99.8)	99.7 (98.2, 100.0)	98.7 (96.7 - 99.6)
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a	A personal history of psychiatric illness (*Correct Response Yes*)	82.5 (77.7, 86.6)	82.8 (78.0, 86.9)	84.0 (79.4, 88.0)	84.5 (80.0 - 88.4)
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response Yes*)	99.3 (97.6, 99.9)	99.0 (97.1, 99.8)	99.7 (98.2, 100.0)	98.7 (96.7 - 99.6)
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
12a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response True*)	97.7 (95.3, 99.1)	96.4 (93.6, 98.2)	97.3 (94.8, 98.8)	94.2 (91.0 - 96.5)

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration					
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]				
12b	TIRF medicines are interchangeable with each other regardless of route of administration (*Correct Response False*)	95.7 (92.8, 97.7)	92.4 (88.8, 95.1)	93.0 (89.5, 95.6)	92.6 (89.1 - 95.2)
12c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response True*)	94.7 (91.5, 96.9)	94.7 (91.5, 96.9)	96.7 (94.0, 98.4)	95.5 (92.5 - 97.5)
12d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response True*)	90.4 (86.5, 93.5)	90.7 (86.9, 93.8)	90.7 (86.8, 93.7)	90.0 (86.1 - 93.1)

Table 16. Correct Response Rates Over Time

48-Month Survey Question Number	Questions as Presented in the 48-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)
16	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. According to the labeling, how should the prescriber proceed? [1]				
16b	The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose (*Correct Response*). [1]	75.5[2]	74.5 (69.2, 79.3)	74.3 (69.0, 79.2)	77.4 (72.4 - 82.0)

[1] Questions presented have been changed from previous survey waves.

[2] 95% confidence interval is not provided since the component was not part of a key risk message during reporting period.

Conclusions

In general, there is an overall trend over time toward increasing improvement in prescriber knowledge and understanding of the key risk messages (Table 16). The consistently high level of prescriber understanding of key risk messages in the latest (48-month) survey indicates that the Education Program for Prescribers is meeting the goals of the TIRF REMS Access Program. Based on prescriber responses, and the high percentage of respondents who indicated they received and read the TIRF REMS Access Program educational materials, the responses may reflect behavior more than knowledge. For the single component that addresses indications for which a TIRF medicine is prescribed, responses may reflect prescriber behavior. That is, prescribers are aware of the labeled indication but choose to prescribe off-label for certain patients. The TRIG will continue to work with the FDA to refine, on a continual basis, the steps to mitigate risks associated with TIRF medicines.

Appendix A Prescriber Survey Protocol Track Change Document: Comparison of 36-month Survey to 48-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Actavis Laboratories FL, Inc.** **BioDelivery Sciences International, Inc. (BDSI) *(replaced* Meda Pharmaceuticals *on March 11, 2015)*** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **Galena Biopharma, Inc.** **Insys Therapeutics, Inc.** **Mallinckrodt Pharmaceuticals** ~~**Meda Pharmaceuticals**~~ **Mylan, Inc.** **Par Pharmaceutical, Inc.**
VERSION:	**10~~7~~.0**
DATE:	**21AUG2015~~25JUL2014~~**
APPROVED:	**FINAL~~Final~~**

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LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access Program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~ ~~,~~ Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI) (replaced Meda Pharmaceuticals on March 11, 2015); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.;~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; and Par Pharmaceutical, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

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.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment form, and Prescribing Information (PI) of each product. This protocol will describe the administration of the surveys that will be conducted among prescribers who are enrolled in the TIRF REMS Access Program. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the following key information and risk messages communicated through 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 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.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers who are enrolled in the TIRF REMS Access Program. Respondents who participate in the previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA provided feedback to the TRIG on the Knowledge, Attitudes, and Behaviors (KAB) survey results for prescribers included in the 12-month REMS Assessment results. The FDA requested that the TRIG investigate the causes for low correct response rates to specific questions in the survey by conducting research to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions. Qualitative research was performed in 2013 prior to Wave 2 of the survey. Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report,

4.1.2 Questions on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions will be presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use “yes” or “no” as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- One question allowing for the respondent to list questions about the products or comments.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use “true” or “yes” vs. “false” or “no” response options, the desired response for key risk messages is generally “true” or “yes” indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are

formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Correct Answer~~Desired response~~**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but ~~have taken opioid therapy before~~	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the ~~labeling for TIRF medicines.~~	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients ~~treated with some fentanyl products.~~	**TRUE**
7c	TIRF medicines may be used to treat opioid non-~~tolerant patients.~~	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose ~~available for that specific product, even if the patient~~ has previously taken another TIRF medicine.	**TRUE**

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:~~**Key Risk Message 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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.~~	
13a~~Question~~	8 mg oral hydromorphone/day~~Question~~	**TRUE~~Desired response~~**

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~~No.~~		
13b	60 mg oral morphine/day	TRUE
13c	30 mg oral oxycodone/day	TRUE
13d	25 mcg transdermal fentanyl/hour	TRUE
13e	25 mg oral oxymorphone/day	TRUE
13f	An equianalgesic dose of another oral opioid	TRUE

Key Risk Message 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®) brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question No.	Question	Desired response
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
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
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	FALSE
9	In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	NO
9b	Headache or migraine pain	NO
9c	Dental pain	NO
9d	Breakthrough pain from cancer	YES
9e	Chronic non-cancer pain	NO
15~~13~~	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	15~~13b~~. 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.
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	

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	each of the following counseling statements.	
20b	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	**TRUE**
20c	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	**FALSE**

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Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Correct Answer~~Desired response~~**
7	Please answer True, False, or I don't know for each statement based on the labeling for ~~TIRF medicines~~.	
7e	It is important to monitor for signs of abuse and addiction in patients who take ~~TIRF medicines~~.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or ~~I don't know for each option~~.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, ~~or a family history of illicit drug use or alcohol abuse~~	**YES**
12~~10~~	Please answer True, False, or I don't know for each statement based on the labeling for ~~TIRF medicines~~.	
12a~~10a~~	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**

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Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question No.	Question	Desired response
12~~10~~	Please answer True, False, or I don't know for each statement based on the labeling for TIRF ~~medicines~~.	
12b~~10b~~	TIRF medicines are interchangeable with each other ~~regardless of route of administration~~.	**FALSE**
12c~~10c~~	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
12d~~10d~~	Dosing of TIRF medicines is not equivalent on a ~~microgram to microgram basis~~.	**TRUE**
16~~14~~	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. According to the~~ labeling, how should the prescriber proceed? Please select one option.	16b~~14b~~. The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis ~~because these~~ medicines have different absorption properties and this could result in a fentanyl overdose.

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4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access Program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following question about behaviors will be asked after the key risk message questions:

Question 1~~12~~3: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of prescribers who are enrolled in the TIRF REMS Access Program will be invited to participate via an invitation letter. The text of the sample written invitation to prescribers can be found in Appendix B. If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of prescribers will be randomly selected.

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All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium to thank them for their participation. Prescribers who practice in Vermont, Massachusetts, or Minnesota and complete the survey will not receive compensation. Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation. The mailing will also include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of prescribers who are invited to participate will be a random sample of all enrolled prescribers. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

Prescribers will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 healthcare providers who are enrolled in the TIRF REMS Access Program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

All prescribers who are enrolled in the TIRF REMS Access Program are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Prescribers who have previously participated in the TIRF REMS KAB survey
- Prescribers or their immediate family members who have ever worked for ever worked for Actavis Laboratories FL, Inc.; Anesta LLC; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of -Teva Pharmaceutical Industries, Ltd); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.;~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; Par Pharmaceutical, Inc.; Teva Pharmaceuticals, Ltd.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Prescriber-identifying information will be stored separately from survey data.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of prescribers who do not have Internet access. It will also be convenient for prescribers to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the prescriber selects to participate in the survey online, he/she will be directed to a secured website to complete screening questions. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any time.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Gender
  - Medical degree of respondent: MD, DO, NP, PA
  - Medical specialty
  - Years of professional experience
  - How many times per month TIRF medicines prescribed in the last 6 months
  - Geographic region of practice

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible prescribers who completed all questions presented to them in the survey ("completers").

7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if there are questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 honorarium, a Thank You Letter, the correct responses to key risk messages, and the ISI after the survey is completed. Respondent contact information is also requested when necessary to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions in addition to instances where a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe TIRF medicines.

Appendix A Prescriber Questionnaire

Survey Legend

- **[PROGRAMMER]** is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

- **(INTERVIEWER)** is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

- **[ONLINE]** indicates a question is worded specifically for administering the survey online.

- **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

- **[BEGIN ~~ONLINE/PHONE~~ SURVEY CONTENT]** and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

- **[TERMINATE]** is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

  Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.

- **[RANDOMIZE LIST]** is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

- Response options for questions that allow multiple responses must be indicated with check boxes (□). At least one option must be selected for the question to be considered answered.

- If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option.~~**[GO TO Qx]** (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.~~

- Response options for questions that allow only one response must be indicated with radio

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Survey Legend

buttons (○).

- If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.
- **[FREE TEXT]** indicates to the programmer that one line should be provided for data entry.
- **[MULTILINE INPUT]** indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).
- **[DROP-DOWN LIST INPUT WITH STATES TABLE]** indicates to the programmer that the response should be a drop-down list containing the states and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

- The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Survey Legend

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
- West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

- The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[BEGIN ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; ~~;~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.; and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. ~~-~~Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[BEGIN PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.;~~,~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc.;~~,~~ and Par Pharmaceutical, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the honorarium after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal

information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call if you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, we cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Are you enrolled in the TIRF REMS Access Program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Actavis Laboratories FL, Inc. **[TERMINATE]**
   - □ Anesta LLC **[TERMINATE]**
   - □ BioDelivery Sciences International, Inc. (BDSI) **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**

- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics, Inc. **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ ~~Meda Pharmaceuticals~~ **[TERMINATE]**
- ☐ Mylan, Inc. **[TERMINATE]**
- ☐ Par Pharmaceutical, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

[RANDOMIZE LIST]	True	False	I don't know
5a. Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b. Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c. Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

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

[RANDOMIZE LIST]	True	False	I don't know
6a. According to the product labeling, a~~A~~ cancer patient may start~~can be started on~~ a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. According to the product labeling, a~~A~~ cancer patient who has been on an around-the-clock opioid for 1 day may~~can~~ start taking a TIRF medicine for breakthrough pain.	○	○	○

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

	[RANDOMIZE LIST]	True	False	I don't know
7a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
7d.	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

[RANDOMIZE LIST]	Yes	No	I don't know
9a. Acute or postoperative pain	○	○	○
9b. Headache or migraine pain	○	○	○
9c. Dental pain	○	○	○
9d. Breakthrough pain from cancer	○	○	○
9e. Chronic non-cancer pain	○	○	○

~~10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.~~

~~[RANDOMIZE LIST]~~	~~True~~	~~False~~	~~I don't know~~

[IF 9E=YES, DISPLAY Q10 and Q11 ON SUBSEQUENT PAGES]

10. For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?

[MULTILINE INPUT]

11. Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?

[MULTILINE INPUT]

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

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
~~10a.~~ TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
~~10b.~~ TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
~~10c.~~ The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○

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~~10d.~~ Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis. ○ ○ ○

~~11.~~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:

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~~[RANDOMIZE LIST]~~	True	False	I don't know
~~11a.~~ 8 mg oral hydromorphone/day	○	○	○
~~11b.~~ 60 mg oral morphine/day	○	○	○
~~11c.~~ 30 mg oral oxycodone/day	○	○	○
~~11d.~~ 25 mcg transdermal fentanyl/hour	○	○	○
~~11e.~~ 25 mg oral oxymorphone/day	○	○	○
~~11f.~~ An equianalgesic dose of another oral opioid	○	○	○

~~12.~~14 How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

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[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
~~12a.~~ Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
~~12b.~~ Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
~~12c.~~ Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
~~12d.~~ Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
~~12e.~~ Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
~~12f.~~1 Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

~~13.~~15. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.

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[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

~~13a.~~1 ○ Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.

~~13b.~~1 ○ 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.

~~13c.~~1 ○ 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.

~~13d.~~1 ○ Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

~~13e.~~1 ○ I don't know

~~14.~~16. 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. According to the labeling, how should the prescriber proceed? Please select one option.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

~~14a.~~1 ○ The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.

~~14b.~~1 ○ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

~~14c.~~1 ○ Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.

~~14d.~~1 ○ 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.

~~14e.~~1 ○ I don't know.

~~15.~~17. A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

~~15a.~~1 ○ An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.

~~15b.~~1 ○ The dose that the prescriber believes is appropriate based on their clinical experience.

~~15c.~~1 ○ The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.

~~15d.~~1 ○ The median available dose.

~~15e.~~1 ○ I don't know.

~~16.~~18. 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? Please pick the best option of the scenarios described.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]~~]~~

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~~16a.~~1 ○ Take another (identical) dose of the TIRF medicine immediately.

~~16b.~~1 ○ Take a dose of an alternative rescue medicine.

~~16c.~~1 ○ Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

~~16d.~~1 ○ Double the dose and take immediately.

~~16e.~~1 ○ I don't know.

~~17.~~19 A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]~~]~~

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~~17a.~~ ○ The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.

~~17b.~~ ○ Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.

~~17c.~~ ○ There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.

~~17d.~~ ○ The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

~~17e.~~ ○ I don't know.

~~18.~~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.

[RANDOMIZE LIST]	True	False	I don't know
~~18a.~~2 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.	○	○	○
~~18b.~~2 Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	○	○	○
~~18c.~~2 Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine~~, they can continue to take their TIRF medicine~~.	○	○	○
~~18d.~~2 Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

~~19. Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?~~

- ~~Yes~~
- ~~No~~

[BEGIN

- ~~I don't know~~

~~[~~PREAMBLE 2 – DISPLAY ON SAME PAGE AS NEXT QUESTION]

The next set of questions is about the educational materials for TIRF medicines and the TIRF Patient-Prescriber Agreement. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®~~, Subsys® and generic versions of any of these brands.

[END PREAMBLE]

~~20.~~21 Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

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- Yes
- No **[GO TO Q23]~~Q22]~~**
- I don't know **[GO TO Q23]~~Q22]~~**

~~21.~~22 Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- Yes
- No
- I don't know

~~22.~~23 Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?

- Yes
- No **[GO TO Q25]~~Q24]~~**
- I don't know **[GO TO Q25]~~Q24]~~**

~~23.~~24 Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?

- Yes
- No
- I don't know

~~24.~~25 Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- Yes
- No **[GO TO Q27~~Q26~~]**
- I don't know **[GO TO Q27~~Q26~~]**

[IF QUESTION 26 = YES, DISPLAY ON SAME PAGE]

~~25.~~26 What are your questions? **[MULTILINE INPUT]**

~~26.~~27 Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?

- Yes
- No **[GO TO DEMOGRAPHICS PREAMBLE 1]~~Q28~~]**
- I don't know **[GO TO DEMOGRAPHICS PREAMBLE 1]~~Q28~~]**

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~~27.~~28 Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?

- Yes
- No
- I don't know

~~28.~~29 Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?

- Yes
- No
- I don't know

[BEGIN DEMOGRAPHICS PREAMBLE 1 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

There are just a few more questions to help us combine your answers with other answers we have received.

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[END DEMOGRAPHICS PREAMBLE 1]

~~29.~~30 On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?

- None **[GO TO DEMOGRAPHICS PREAMBLE 2]**
- 1 – 2 times per month
- 3 – 5 times per month
- More than 5 times per month
- I don't remember

~~30.~~31 Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ ~~Onsolis®~~
- ☐ Subsys®

[BEGIN DEMOGRAPHICS PREAMBLE 2 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

These last few questions are for demographic purposes.

[END DEMOGRAPHICS PREAMBLE 2]

~~31.~~32 What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

~~32.~~33 What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner
- ○ Physician Assistant
- ○ Prefer not to answer

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~~33.~~34 In total, how many years have you been practicing medicine, since completing your education?

- Less than 3 years
- 3 – 5 years
- 6 – 10 years
- 11 – 15 years
- More than 15 years
- Prefer not to answer

35. Do you practice in a closed healthcare system, such as: (b) (4) , VA, DoD, or NIH?

- Yes
- No

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~~34.~~36 In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

~~35.~~37 What is your medical specialty?

- Oncology
- Primary care
- Pain management
- Other (please specify): **[FREE TEXT]**
- No designated specialty

[PHONE ~~ONLY:~~ BEGIN ADVERSE EVENT/PRODUCT COMPLAINT – KEEP ON ONE PAGE]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- Yes

- No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[BEGIN CLOSING 1 – KEEP ON ONE PAGE]

We would like to send you a $125 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey. As a reminder, physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- Yes
- No **[GO~~SKIP~~ TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[MUST BE 5 NUMERIC CHARACTERS ONLY]**

[END CLOSING 1]

[BEGIN ~~[~~CLOSING 2 – KEEP ON ONE PAGE]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- ○ Yes
- ○ No [GO~~SKIP~~ TO CLOSING 3]

Telephone: [MUST BE 10-DIGIT NUMERIC-ONLY CHARACTERS]

[END CLOSING 2]

[BEGIN CLOSING 3]

That ends the survey. Thank you again for your help.

[END CLOSING 3]

[END~~OF~~ SURVEY CONTENT]

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Appendix B SAMPLE Prescriber Invitation Letter

[CURR_DATE]

[PRESCRIBER NAME]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [PRESCRIBER NAME]:

You were selected to receive this letter because you have enrolled in the TIRF REMS Access Program. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, ~~Onsolis®,~~ Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines (collectively referred to as the "TIRF REMS Industry ~~-~~Group") include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; ~~:~~ Mallinckrodt Pharmaceuticals; ~~Meda Pharmaceuticals;~~ Mylan, Inc., and Par Pharmaceutical, Inc. These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and if required to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Prescribers who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating, go to **www.TIRFREMSsurvey~~XXXXXXXXXX~~.com** anytime or call **1-877-379-3297,** 8AM to 8PM Eastern Time Monday through Friday. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.

* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Please have this letter with you at the time you take the survey. Thank you in advance for your help with this important effort.

Sincerely,

The TIRF REMS Survey Team

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1-877-379-3297

www.TIRFREMSsurvey.com

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Appendix B Prescriber Survey Listings and Stratified Analyses Tables

Listing 1.1 and Listing 2.1 includes individual responses to Question 10 (*For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?*), and Question 11 (*Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?*), respectively. Aggregate data for Question 10 is provided in Table 9 and aggregate data for Question 11 is provided in Table 10. The verbatim responses are provided unedited as submitted by the prescriber.

Table 1.1: Survey Administration Statistics

Parameter, n (%)	
Number of invitations distributed	8210
Number of invitations returned as undeliverable	437
Number of reminder letters distributed	19215
All Respondents[1]	587 (7.6)
Eligible Respondents[2]	350 (59.6)
Completed survey[3]	310 (88.6)
Did not complete the survey[3]	40 (11.4)
Respondents not eligible[2][4]	237 (40.4)

[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentages are based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Prescribers (N=587) n (%)
Question 1: Do you agree to participate in this survey?	
Yes	485 (82.6)
No[1]	4 (0.7)
Discontinued	98 (16.7)
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.	
Yes[1]	30 (5.1)
No	399 (68.0)
I don't know[1]	56 (9.5)
Question not asked [2]	4 (0.7)
Discontinued	98 (16.7)
Question 3: Are you enrolled in the TIRF REMS Access Program?	
Yes	366 (62.4)
No[1]	17 (2.9)
I don't know[1]	14 (2.4)
Question not asked [2]	90 (15.3)
Discontinued	100 (17.0)
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.	
Actavis Laboratories FL, Inc.[1]	1 (0.2)
Anesta, LLC[1]	0
BioDelivery Services International, Inc. (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	3 (0.5)
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	5 (0.9)
Mallinckrodt Pharmaceuticals[1]	0
McKesson Specialty Care Solutions[1]	0
Mylan, Inc.[1]	0

Table 1.2: Survey Participant Eligibility Results - All Respondents

Question	Prescribers (N=587) n (%)
Par Pharmaceutical, Inc.[1]	0
RelayHealth[1]	0
Teva Pharmaceuticals, Ltd.[1]	2 (0.3)
United BioSource Corporation[1]	0
FDA[1]	0
None of these apply[3]	350 (59.6)
I don't know[1]	3 (0.5)
Prefer not to answer[1]	3 (0.5)
Question not asked [2]	121 (20.6)
Discontinued	100 (17.0)

[1] Ineligible to participate in the survey.
[2] Question not asked due to previous question termination.
[3] Ineligible to participate in the survey if selected in addition to another response.
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.

Table 1.3: Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total
Summary Statistic (minutes)			
N	7	303	310
Mean (SD)	25.37 (4.816)	16.33 (7.797)	16.54 (7.853)
Minimum	20.1	4.0	4.0
Median	25.05	15.00	15.10
Maximum	35.3	60.4	60.4
Category, n			
0 to <5 Minutes	0	1	1
5 to <10 Minutes	0	59	59
10 to <15 Minutes	0	91	91
15 to <20 Minutes	0	85	85
20 to <25 Minutes	3	37	40
25 to <30 Minutes	3	12	15
30 Minutes or more	1	18	19

Table 2: Description of Eligible Prescribers - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 30: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?	
None	77 (24.8)
1 - 2 times per month	154 (49.7)
3 - 5 times per month	49 (15.8)
More than 5 times per month	17 (5.5)
I don't remember	13 (4.2)
Question 31: Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.[1]	
Abstral®	26 (11.2)
Actiq® or generic Actiq®	137 (58.8)
Fentora®	94 (40.3)
Lazanda®	22 (9.4)
Subsys®	105 (45.1)
N/A (Answered "None" to Question 30)	77
Question 32: What is your gender?	
Male	192 (61.9)
Female	116 (37.4)
Prefer not to answer	2 (0.6)
Question 33: What is your medical degree?	
MD	178 (57.4)
DO	26 (8.4)
Nurse Practitioner	68 (21.9)
Physician Assistant	35 (11.3)
Prefer not to answer	3 (1.0)
Question 34: In total, how many years have you been practicing medicine, since completing your education?	
Less than 3 years	41 (13.2)
3 - 5 years	38 (12.3)
6 - 10 years	71 (22.9)

Table 2: Description of Eligible Prescribers - Completed Surveys

Question	Prescribers (N=310) n (%)
11 - 15 years	51 (16.5)
More than 15 years	107 (34.5)
Prefer not to answer	2 (0.6)
Question 35: Do you practice in a closed healthcare system, such as: (b) (4) VA, DoD, or NIH?	
Yes	14 (4.5)
No	296 (95.5)
Geographic Distribution (based on Question 36 - In which state do you practice?)[2]	
Northeast	70 (22.6)
Midwest	46 (14.8)
South	97 (31.3)
West	95 (30.6)
Other	1 (0.3)
Prefer not to answer	1 (0.3)
Question 37: What is your medical specialty?	
Oncology	65 (21.0)
Primary care	28 (9.0)
Pain management	151 (48.7)
Other (please specify):[3]	65 (21.0)
No designated specialty	1 (0.3)

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[3] Verbatim texts for question about medical specialty will be presented in Listing 4.

Table 2a: Comparison of Survey Respondents to General Population of TIRF Prescribers

Question	Eligible/Completed Prescribers (N=310) n (%)	Prescribers of TIRF Medicines in the Past 6 Months[1] (N=8812) n (%)
Geographic Distribution[2]		
Northeast	70 (22.6)	1854 (21.0)
Midwest	46 (14.8)	1532 (17.4)
South	97 (31.3)	3047 (34.6)
West	95 (30.6)	2374 (26.9)
Other	1 (0.3)	5 (0.1)
Prefer not to answer	1 (0.3)	0

[1] Based on data obtained from the TIRF REMS Access Program database.
[2] Based on Prescriber KAB Survey Question 36; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
Note: Percentages are based on the prescribers with informative data.

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[1]	295 (95.2)
False	14 (4.5)
I don't know	1 (0.3)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	15 (4.8)
False[1]	291 (93.9)
I don't know	4 (1.3)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	33 (10.6)
False[1]	269 (86.8)
I don't know	8 (2.6)
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	75 (24.2)
False[1]	214 (69.0)
I don't know	21 (6.8)
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.	
True	62 (20.0)
False[1]	226 (72.9)
I don't know	22 (7.1)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[1]	280 (90.3)
False	23 (7.4)
I don't know	7 (2.3)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[1]	298 (96.1)
False	2 (0.6)
I don't know	10 (3.2)
7c: TIRF medicines may be used in opioid non-tolerant patients.	
True	38 (12.3)
False[1]	263 (84.8)
I don't know	9 (2.9)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[1]	265 (85.5)
False	40 (12.9)
I don't know	5 (1.6)
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[1]	306 (98.7)
False	2 (0.6)
I don't know	2 (0.6)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[1]	262 (84.5)
No	28 (9.0)
I don't know	20 (6.5)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
Yes[1]	306 (98.7)
No	4 (1.3)
I don't know	0
8c: A family history of asthma	
Yes	12 (3.9)
No[1]	281 (90.6)
I don't know	17 (5.5)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	28 (9.0)
No[1]	280 (90.3)
I don't know	2 (0.6)
9b: Headache or migraine pain	
Yes	16 (5.2)
No[1]	294 (94.8)
I don't know	0
9c: Dental pain	
Yes	5 (1.6)
No[1]	305 (98.4)
I don't know	0
9d: Breakthrough pain from cancer	
Yes[1]	288 (92.9)
No	22 (7.1)
I don't know	0
9e: Chronic non-cancer pain	
Yes[2]	106 (34.2)
No[1]	201 (64.8)
I don't know	3 (1.0)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[1]	292 (94.2)
False	12 (3.9)
I don't know	6 (1.9)
12b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	13 (4.2)
False[1]	287 (92.6)
I don't know	10 (3.2)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[1]	296 (95.5)
False	6 (1.9)
I don't know	8 (2.6)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[1]	279 (90.0)
False	21 (6.8)
I don't know	10 (3.2)
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:	
13a: 8 mg oral hydromorphone/day	
True[1]	226 (72.9)
False	57 (18.4)
I don't know	27 (8.7)
13b: 60 mg oral morphine/day	
True[1]	293 (94.5)
False	11 (3.5)
I don't know	6 (1.9)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
13c: 30 mg oral oxycodone/day	
True[1]	244 (78.7)
False	46 (14.8)
I don't know	20 (6.5)
13d: 25 mcg transdermal fentanyl/hour	
True[1]	265 (85.5)
False	27 (8.7)
I don't know	18 (5.8)
13e: 25 mg oral oxymorphone/day	
True[1]	224 (72.3)
False	33 (10.6)
I don't know	53 (17.1)
13f: An equianalgesic dose of another oral opioid	
True[1]	210 (67.7)
False	55 (17.7)
I don't know	45 (14.5)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	26 (8.4)
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.[1]	227 (73.2)
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.	18 (5.8)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	19 (6.1)
I don't know	20 (6.5)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 16: 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. According to the labeling, how should the prescriber proceed? Please select one option.	
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	3 (1.0)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[1]	240 (77.4)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	22 (7.1)
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.	33 (10.6)
I don't know.	12 (3.9)
Question 17: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.	
An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	35 (11.3)
The dose that the prescriber believes is appropriate based on their clinical experience.	3 (1.0)
The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.[1]	267 (86.1)
The median available dose.	2 (0.6)
I don't know.	3 (1.0)
Question 18: 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? Please pick the best option of the scenarios described.	
Take another (identical) dose of the TIRF medicine immediately.	78 (25.2)
Take a dose of an alternative rescue medicine.	13 (4.2)
Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.[1]	213 (68.7)
Double the dose and take immediately.	5 (1.6)
I don't know.	1 (0.3)
Question 19: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	14 (4.5)
Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.[1]	235 (75.8)
There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	6 (1.9)
The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.	10 (3.2)
I don't know.	45 (14.5)
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.	
20a: 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.	
True[1]	308 (99.4)
False	1 (0.3)
I don't know	1 (0.3)
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	
True[1]	291 (93.9)
False	12 (3.9)
I don't know	7 (2.3)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	
True	64 (20.6)
False[1]	226 (72.9)
I don't know	20 (6.5)
20d: Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	
True[1]	309 (99.7)
False	0

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
I don't know	1 (0.3)

[1] Correct response.
[2] Verbatim for the type of chronic non-cancer pain and reason for selecting TIRF medicines to treat chronic non-cancer pain are presented in Listing 1 and Listing 2.

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 21: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?	
Yes	286 (92.3)
No	9 (2.9)
I don't know	15 (4.8)
Question 22: Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?[1]	
Yes	238 (83.2)
No	41 (14.3)
I don't know	7 (2.4)
N/A (Answered "No" or "I don't know" to Question 21)	24
Question 23: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?	
Yes	276 (89.0)
No	10 (3.2)
I don't know	24 (7.7)
Question 24: Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?[1]	
Yes	257 (93.1)
No	14 (5.1)
I don't know	5 (1.8)
N/A (Answered "No" or "I don't know" to Question 23)	34
Question 25: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?	
Yes[2]	12 (3.9)
No	272 (87.7)
I don't know	26 (8.4)

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim texts for question about the Medication Guide are presented in Listing 3.

Table 5: Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 27: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?	
Yes	286 (92.3)
No	17 (5.5)
I don't know	7 (2.3)
Question 28: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?[1]	
Yes	266 (93.0)
No	9 (3.1)
I don't know	11 (3.8)
N/A (Answered "No" or "I don't know" to Question 27)	24
Question 29: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?[1]	
Yes	249 (87.1)
No	21 (7.3)
I don't know	16 (5.6)
N/A (Answered "No" or "I don't know" to Question 27)	24

[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

Table 6: Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
Question 14: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
14a: Ask patients (or their caregivers) about the presence of children in the home	
Always	178 (57.4)
Only with the first prescription	75 (24.2)
Sometimes	42 (13.5)
Never	11 (3.5)
I don't know	4 (1.3)
14b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	
Always	249 (80.3)
Only with the first prescription	43 (13.9)
Sometimes	13 (4.2)
Never	3 (1.0)
I don't know	2 (0.6)
14c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	
Always	203 (65.5)
Only with the first prescription	66 (21.3)
Sometimes	27 (8.7)
Never	11 (3.5)
I don't know	3 (1.0)
14d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	
Always	220 (71.0)
Only with the first prescription	61 (19.7)
Sometimes	19 (6.1)
Never	7 (2.3)
I don't know	3 (1.0)
14e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	

Table 6: Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys

Question	Prescribers (N=310) n (%)
Always	190 (61.3)
Only with the first prescription	74 (23.9)
Sometimes	37 (11.9)
Never	6 (1.9)
I don't know	3 (1.0)
14f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine	
Always	140 (45.2)
Only with the first prescription	123 (39.7)
Sometimes	23 (7.4)
Never	21 (6.8)
I don't know	3 (1.0)

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Prescribers (N=310) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[2]	295 (95.2) [92.1 - 97.3]
False	14 (4.5)
I don't know	1 (0.3)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	15 (4.8)
False[2]	291 (93.9) [90.6 - 96.3]
I don't know	4 (1.3)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	33 (10.6)
False[2]	269 (86.8) [82.5 - 90.3]
I don't know	8 (2.6)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[2]	280 (90.3) [86.5 - 93.4]
False	23 (7.4)
I don't know	7 (2.3)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[2]	298 (96.1) [93.3 - 98.0]
False	2 (0.6)
I don't know	10 (3.2)
7c: TIRF medicines may be used in opioid non-tolerant patients.	

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Prescribers (N=310) n (%) [95% CI][1]
True	38 (12.3)
False[2]	263 (84.8) [80.4 - 88.6]
I don't know	9 (2.9)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[2]	265 (85.5) [81.1 - 89.2]
False	40 (12.9)
I don't know	5 (1.6)
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:	
13a: 8 mg oral hydromorphone/day	
True[2]	226 (72.9) [67.6 - 77.8]
False	57 (18.4)
I don't know	27 (8.7)
13b: 60 mg oral morphine/day	
True[2]	293 (94.5) [91.4 - 96.8]
False	11 (3.5)
I don't know	6 (1.9)
13c: 30 mg oral oxycodone/day	
True[2]	244 (78.7) [73.7 - 83.1]
False	46 (14.8)
I don't know	20 (6.5)
13d: 25 mcg transdermal fentanyl/hour	
True[2]	265 (85.5) [81.1 - 89.2]
False	27 (8.7)
I don't know	18 (5.8)

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Prescribers (N=310) n (%) [95% CI][1]
13e: 25 mg oral oxymorphone/day	
True[2]	224 (72.3) [66.9 - 77.2]
False	33 (10.6)
I don't know	53 (17.1)
13f: An equianalgesic dose of another oral opioid	
True[2]	210 (67.7) [62.2 - 72.9]
False	55 (17.7)
I don't know	45 (14.5)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True[2]	170 (95.5) [91.3 - 98.0]	26 (100.0) [86.8 - 100.0]	63 (92.6) [83.7 - 97.6]	33 (94.3) [80.8 - 99.3]
False	8 (4.5)	0	4 (5.9)	2 (5.7)
I don't know	0	0	1 (1.5)	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
True	10 (5.6)	1 (3.8)	4 (5.9)	0
False[2]	165 (92.7) [87.8 - 96.1]	25 (96.2) [80.4 - 99.9]	63 (92.6) [83.7 - 97.6]	35 (100.0) [90.0 - 100.0]
I don't know	3 (1.7)	0	1 (1.5)	0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
True	17 (9.6)	4 (15.4)	10 (14.7)	2 (5.7)
False[2]	156 (87.6) [81.9 - 92.1]	21 (80.8) [60.6 - 93.4]	57 (83.8) [72.9 - 91.6]	32 (91.4) [76.9 - 98.2]
I don't know	5 (2.8)	1 (3.8)	1 (1.5)	1 (2.9)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
True[2]	162 (91.0) [85.8 - 94.8]	24 (92.3) [74.9 - 99.1]	59 (86.8) [76.4 - 93.8]	33 (94.3) [80.8 - 99.3]
False	13 (7.3)	2 (7.7)	7 (10.3)	1 (2.9)
I don't know	3 (1.7)	0	2 (2.9)	1 (2.9)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True[2]	173 (97.2) [93.6 - 99.1]	24 (92.3) [74.9 - 99.1]	66 (97.1) [89.8 - 99.6]	33 (94.3) [80.8 - 99.3]
False	2 (1.1)	0	0	0
I don't know	3 (1.7)	2 (7.7)	2 (2.9)	2 (5.7)
7c: TIRF medicines may be used in opioid non-tolerant patients.				
True	23 (12.9)	3 (11.5)	8 (11.8)	3 (8.6)
False[2]	150 (84.3) [78.1 - 89.3]	22 (84.6) [65.1 - 95.6]	57 (83.8) [72.9 - 91.6]	32 (91.4) [76.9 - 98.2]
I don't know	5 (2.8)	1 (3.8)	3 (4.4)	0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True[2]	152 (85.4) [79.3 - 90.2]	24 (92.3) [74.9 - 99.1]	56 (82.4) [71.2 - 90.5]	31 (88.6) [73.3 - 96.8]
False	23 (12.9)	2 (7.7)	10 (14.7)	4 (11.4)
I don't know	3 (1.7)	0	2 (2.9)	0

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
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:				
13a: 8 mg oral hydromorphone/day				
True[2]	135 (75.8) [68.9 - 81.9]	18 (69.2) [48.2 - 85.7]	43 (63.2) [50.7 - 74.6]	27 (77.1) [59.9 - 89.6]
False	26 (14.6)	7 (26.9)	20 (29.4)	4 (11.4)
I don't know	17 (9.6)	1 (3.8)	5 (7.4)	4 (11.4)
13b: 60 mg oral morphine/day				
True[2]	165 (92.7) [87.8 - 96.1]	25 (96.2) [80.4 - 99.9]	65 (95.6) [87.6 - 99.1]	35 (100.0) [90.0 - 100.0]
False	8 (4.5)	1 (3.8)	2 (2.9)	0
I don't know	5 (2.8)	0	1 (1.5)	0
13c: 30 mg oral oxycodone/day				
True[2]	143 (80.3) [73.7 - 85.9]	22 (84.6) [65.1 - 95.6]	47 (69.1) [56.7 - 79.8]	29 (82.9) [66.4 - 93.4]
False	23 (12.9)	4 (15.4)	14 (20.6)	5 (14.3)
I don't know	12 (6.7)	0	7 (10.3)	1 (2.9)
13d: 25 mcg transdermal fentanyl/hour				
True[2]	153 (86.0) [80.0 - 90.7]	22 (84.6) [65.1 - 95.6]	54 (79.4) [67.9 - 88.3]	33 (94.3) [80.8 - 99.3]

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
False	14 (7.9)	3 (11.5)	9 (13.2)	1 (2.9)
I don't know	11 (6.2)	1 (3.8)	5 (7.4)	1 (2.9)
13e: 25 mg oral oxymorphone/day				
True[2]	127 (71.3) [64.1 - 77.9]	16 (61.5) [40.6 - 79.8]	47 (69.1) [56.7 - 79.8]	31 (88.6) [73.3 - 96.8]
False	17 (9.6)	6 (23.1)	8 (11.8)	2 (5.7)
I don't know	34 (19.1)	4 (15.4)	13 (19.1)	2 (5.7)
13f: An equianalgesic dose of another oral opioid				
True[2]	126 (70.8) [63.5 - 77.3]	18 (69.2) [48.2 - 85.7]	43 (63.2) [50.7 - 74.6]	21 (60.0) [42.1 - 76.1]
False	27 (15.2)	4 (15.4)	15 (22.1)	9 (25.7)
I don't know	25 (14.0)	4 (15.4)	10 (14.7)	5 (14.3)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True[2]	37 (90.2) [76.9 - 97.3]	36 (94.7) [82.3 - 99.4]	117 (95.9) [90.7 - 98.7]	103 (96.3) [90.7 - 99.0]
False	3 (7.3)	2 (5.3)	5 (4.1)	4 (3.7)
I don't know	1 (2.4)	0	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
True	0	0	6 (4.9)	9 (8.4)
False[2]	41 (100.0) [91.4 - 100.0]	38 (100.0) [90.7 - 100.0]	113 (92.6) [86.5 - 96.6]	97 (90.7) [83.5 - 95.4]
I don't know	0	0	3 (2.5)	1 (0.9)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
True	2 (4.9)	4 (10.5)	11 (9.0)	15 (14.0)
False[2]	39 (95.1) [83.5 - 99.4]	32 (84.2) [68.7 - 94.0]	109 (89.3) [82.5 - 94.2]	88 (82.2) [73.7 - 89.0]
I don't know	0	2 (5.3)	2 (1.6)	4 (3.7)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
True[2]	36 (87.8) [73.8 - 95.9]	34 (89.5) [75.2 - 97.1]	109 (89.3) [82.5 - 94.2]	100 (93.5) [87.0 - 97.3]
False	4 (9.8)	2 (5.3)	11 (9.0)	5 (4.7)
I don't know	1 (2.4)	2 (5.3)	2 (1.6)	2 (1.9)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True[2]	40 (97.6) [87.1 - 99.9]	35 (92.1) [78.6 - 98.3]	117 (95.9) [90.7 - 98.7]	104 (97.2) [92.0 - 99.4]
False	0	0	1 (0.8)	1 (0.9)
I don't know	1 (2.4)	3 (7.9)	4 (3.3)	2 (1.9)
7c: TIRF medicines may be used in opioid non-tolerant patients.				
True	5 (12.2)	4 (10.5)	17 (13.9)	11 (10.3)
False[2]	36 (87.8) [73.8 - 95.9]	32 (84.2) [68.7 - 94.0]	100 (82.0) [74.0 - 88.3]	94 (87.9) [80.1 - 93.4]
I don't know	0	2 (5.3)	5 (4.1)	2 (1.9)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True[2]	34 (82.9) [67.9 - 92.8]	31 (81.6) [65.7 - 92.3]	105 (86.1) [78.6 - 91.7]	93 (86.9) [79.0 - 92.7]
False	5 (12.2)	6 (15.8)	15 (12.3)	14 (13.1)
I don't know	2 (4.9)	1 (2.6)	2 (1.6)	0

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
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:				
13a: 8 mg oral hydromorphone/day				
True[2]	27 (65.9) [49.4 - 79.9]	30 (78.9) [62.7 - 90.4]	84 (68.9) [59.8 - 76.9]	84 (78.5) [69.5 - 85.9]
False	8 (19.5)	6 (15.8)	29 (23.8)	13 (12.1)
I don't know	6 (14.6)	2 (5.3)	9 (7.4)	10 (9.3)
13b: 60 mg oral morphine/day				
True[2]	37 (90.2) [76.9 - 97.3]	37 (97.4) [86.2 - 99.9]	117 (95.9) [90.7 - 98.7]	100 (93.5) [87.0 - 97.3]
False	2 (4.9)	0	4 (3.3)	5 (4.7)
I don't know	2 (4.9)	1 (2.6)	1 (0.8)	2 (1.9)
13c: 30 mg oral oxycodone/day				
True[2]	29 (70.7) [54.5 - 83.9]	31 (81.6) [65.7 - 92.3]	95 (77.9) [69.5 - 84.9]	88 (82.2) [73.7 - 89.0]
False	8 (19.5)	5 (13.2)	21 (17.2)	11 (10.3)
I don't know	4 (9.8)	2 (5.3)	6 (4.9)	8 (7.5)
13d: 25 mcg transdermal fentanyl/hour				
True[2]	34 (82.9) [67.9 - 92.8]	32 (84.2) [68.7 - 94.0]	103 (84.4) [76.8 - 90.4]	94 (87.9) [80.1 - 93.4]

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
False	2 (4.9)	5 (13.2)	12 (9.8)	8 (7.5)
I don't know	5 (12.2)	1 (2.6)	7 (5.7)	5 (4.7)
13e: 25 mg oral oxymorphone/day				
True[2]	31 (75.6) [59.7 - 87.6]	28 (73.7) [56.9 - 86.6]	89 (73.0) [64.2 - 80.6]	75 (70.1) [60.5 - 78.6]
False	0	4 (10.5)	16 (13.1)	12 (11.2)
I don't know	10 (24.4)	6 (15.8)	17 (13.9)	20 (18.7)
13f: An equianalgesic dose of another oral opioid				
True[2]	26 (63.4) [46.9 - 77.9]	27 (71.1) [54.1 - 84.6]	82 (67.2) [58.1 - 75.4]	74 (69.2) [59.5 - 77.7]
False	9 (22.0)	5 (13.2)	22 (18.0)	18 (16.8)
I don't know	6 (14.6)	6 (15.8)	18 (14.8)	15 (14.0)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:					
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer					
True[2]	76 (98.7) [93.0 - 100.0]	144 (93.5) [88.4 - 96.8]	46 (93.9) [83.1 - 98.7]	16 (94.1) [71.3 - 99.9]	13 (100.0) [75.3 - 100.0]
False	1 (1.3)	9 (5.8)	3 (6.1)	1 (5.9)	0
I don't know	0	1 (0.6)	0	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before					
True	3 (3.9)	7 (4.5)	2 (4.1)	3 (17.6)	0
False[2]	73 (94.8) [87.2 - 98.6]	145 (94.2) [89.2 - 97.3]	46 (93.9) [83.1 - 98.7]	14 (82.4) [56.6 - 96.2]	13 (100.0) [75.3 - 100.0]
I don't know	1 (1.3)	2 (1.3)	1 (2.0)	0	0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy					
True	8 (10.4)	13 (8.4)	6 (12.2)	4 (23.5)	2 (15.4)
False[2]	67 (87.0) [77.4 - 93.6]	136 (88.3) [82.2 - 92.9]	43 (87.8) [75.2 - 95.4]	13 (76.5) [50.1 - 93.2]	10 (76.9) [46.2 - 95.0]
I don't know	2 (2.6)	5 (3.2)	0	0	1 (7.7)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.					
True[2]	65 (84.4) [74.4 - 91.7]	141 (91.6) [86.0 - 95.4]	46 (93.9) [83.1 - 98.7]	16 (94.1) [71.3 - 99.9]	12 (92.3) [64.0 - 99.8]
False	10 (13.0)	9 (5.8)	2 (4.1)	1 (5.9)	1 (7.7)
I don't know	2 (2.6)	4 (2.6)	1 (2.0)	0	0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.					
True[2]	76 (98.7) [93.0 - 100.0]	147 (95.5) [90.9 - 98.2]	47 (95.9) [86.0 - 99.5]	16 (94.1) [71.3 - 99.9]	12 (92.3) [64.0 - 99.8]
False	0	0	1 (2.0)	1 (5.9)	0
I don't know	1 (1.3)	7 (4.5)	1 (2.0)	0	1 (7.7)
7c: TIRF medicines may be used in opioid non-tolerant patients.					
True	11 (14.3)	19 (12.3)	4 (8.2)	3 (17.6)	1 (7.7)
False[2]	64 (83.1) [72.9 - 90.7]	130 (84.4) [77.7 - 89.8]	44 (89.8) [77.8 - 96.6]	13 (76.5) [50.1 - 93.2]	12 (92.3) [64.0 - 99.8]
I don't know	2 (2.6)	5 (3.2)	1 (2.0)	1 (5.9)	0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.					
True[2]	68 (88.3) [79.0 - 94.5]	132 (85.7) [79.2 - 90.8]	40 (81.6) [68.0 - 91.2]	16 (94.1) [71.3 - 99.9]	9 (69.2) [38.6 - 90.9]

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
False	9 (11.7)	18 (11.7)	9 (18.4)	1 (5.9)	3 (23.1)
I don't know	0	4 (2.6)	0	0	1 (7.7)
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:					
13a: 8 mg oral hydromorphone/day					
True[2]	54 (70.1) [58.6 - 80.0]	109 (70.8) [62.9 - 77.8]	38 (77.6) [63.4 - 88.2]	14 (82.4) [56.6 - 96.2]	11 (84.6) [54.6 - 98.1]
False	14 (18.2)	31 (20.1)	7 (14.3)	3 (17.6)	2 (15.4)
I don't know	9 (11.7)	14 (9.1)	4 (8.2)	0	0
13b: 60 mg oral morphine/day					
True[2]	70 (90.9) [82.2 - 96.3]	145 (94.2) [89.2 - 97.3]	49 (100.0) [92.7 - 100.0]	17 (100.0) [80.5 - 100.0]	12 (92.3) [64.0 - 99.8]
False	3 (3.9)	7 (4.5)	0	0	1 (7.7)
I don't know	4 (5.2)	2 (1.3)	0	0	0
13c: 30 mg oral oxycodone/day					
True[2]	58 (75.3) [64.2 - 84.4]	120 (77.9) [70.5 - 84.2]	44 (89.8) [77.8 - 96.6]	13 (76.5) [50.1 - 93.2]	9 (69.2) [38.6 - 90.9]
False	11 (14.3)	24 (15.6)	4 (8.2)	4 (23.5)	3 (23.1)

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
I don't know	8 (10.4)	10 (6.5)	1 (2.0)	0	1 (7.7)
13d: 25 mcg transdermal fentanyl/hour					
True[2]	65 (84.4) [74.4 - 91.7]	135 (87.7) [81.4 - 92.4]	41 (83.7) [70.3 - 92.7]	14 (82.4) [56.6 - 96.2]	10 (76.9) [46.2 - 95.0]
False	4 (5.2)	11 (7.1)	6 (12.2)	3 (17.6)	3 (23.1)
I don't know	8 (10.4)	8 (5.2)	2 (4.1)	0	0
13e: 25 mg oral oxymorphone/day					
True[2]	49 (63.6) [51.9 - 74.3]	109 (70.8) [62.9 - 77.8]	41 (83.7) [70.3 - 92.7]	14 (82.4) [56.6 - 96.2]	11 (84.6) [54.6 - 98.1]
False	6 (7.8)	20 (13.0)	4 (8.2)	3 (17.6)	0
I don't know	22 (28.6)	25 (16.2)	4 (8.2)	0	2 (15.4)
13f: An equianalgesic dose of another oral opioid					
True[2]	51 (66.2) [54.6 - 76.6]	107 (69.5) [61.6 - 76.6]	30 (61.2) [46.2 - 74.8]	13 (76.5) [50.1 - 93.2]	9 (69.2) [38.6 - 90.9]
False	12 (15.6)	28 (18.2)	12 (24.5)	1 (5.9)	2 (15.4)
I don't know	14 (18.2)	19 (12.3)	7 (14.3)	3 (17.6)	2 (15.4)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Key Risk Message #1: TIRF medicines are contraindicated in opioid non-tolerant patients.

Correct Responses	Prescribers (N=310) n (%) [95% CI][1]
0 correct responses	0
1 correct response	0
2 correct responses	1 (0.3)
3 correct responses	1 (0.3)
4 correct responses	1 (0.3)
5 correct responses	0
6 correct responses	7 (2.3)
7 correct responses	10 (3.2)
8 correct responses	21 (6.8)
9 correct responses	23 (7.4)
10 correct responses	36 (11.6)
11 correct responses	47 (15.2)
12 correct responses	69 (22.3)
13 correct responses	94 (30.3) [25.3 - 35.8]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Prescribers (N=310) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	75 (24.2)
False[2]	214 (69.0) [63.6 - 74.1]
I don't know	21 (6.8)
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.	
True	62 (20.0)
False[2]	226 (72.9) [67.6 - 77.8]
I don't know	22 (7.1)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	28 (9.0)
No[2]	280 (90.3) [86.5 - 93.4]
I don't know	2 (0.6)
9b: Headache or migraine pain	
Yes	16 (5.2)
No[2]	294 (94.8) [91.8 - 97.0]
I don't know	0
9c: Dental pain	
Yes	5 (1.6)
No[2]	305 (98.4) [96.3 - 99.5]
I don't know	0

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Prescribers (N=310) n (%) [95% CI][1]
9d: Breakthrough pain from cancer	
Yes[2]	288 (92.9) [89.5 - 95.5]
No	22 (7.1)
I don't know	0
9e: Chronic non-cancer pain	
Yes	106 (34.2)
No[2]	201 (64.8) [59.2 - 70.2]
I don't know	3 (1.0)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	26 (8.4)
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.[2]	227 (73.2) [67.9 - 78.1]
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.	18 (5.8)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	19 (6.1)
I don't know	20 (6.5)
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.	
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	
True[2]	291 (93.9) [90.6 - 96.3]
False	12 (3.9)

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Prescribers (N=310) n (%) [95% CI][1]
I don't know	7 (2.3)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	
True	64 (20.6)
False[2]	226 (72.9) [67.6 - 77.8]
I don't know	20 (6.5)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.				
True	45 (25.3)	8 (30.8)	14 (20.6)	7 (20.0)
False[2]	122 (68.5) [61.2 - 75.3]	18 (69.2) [48.2 - 85.7]	47 (69.1) [56.7 - 79.8]	26 (74.3) [56.7 - 87.5]
I don't know	11 (6.2)	0	7 (10.3)	2 (5.7)
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.				
True	37 (20.8)	9 (34.6)	11 (16.2)	4 (11.4)
False[2]	130 (73.0) [65.9 - 79.4]	16 (61.5) [40.6 - 79.8]	50 (73.5) [61.4 - 83.5]	28 (80.0) [63.1 - 91.6]
I don't know	11 (6.2)	1 (3.8)	7 (10.3)	3 (8.6)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
Yes	21 (11.8)	1 (3.8)	5 (7.4)	1 (2.9)
No[2]	157 (88.2) [82.5 - 92.5]	25 (96.2) [80.4 - 99.9]	61 (89.7) [79.9 - 95.8]	34 (97.1) [85.1 - 99.9]

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
I don't know	0	0	2 (2.9)	0
9b: Headache or migraine pain				
Yes	11 (6.2)	1 (3.8)	2 (2.9)	2 (5.7)
No[2]	167 (93.8) [89.2 - 96.9]	25 (96.2) [80.4 - 99.9]	66 (97.1) [89.8 - 99.6]	33 (94.3) [80.8 - 99.3]
I don't know	0	0	0	0
9c: Dental pain				
Yes	5 (2.8)	0	0	0
No[2]	173 (97.2) [93.6 - 99.1]	26 (100.0) [86.8 - 100.0]	68 (100.0) [94.7 - 100.0]	35 (100.0) [90.0 - 100.0]
I don't know	0	0	0	0
9d: Breakthrough pain from cancer				
Yes[2]	167 (93.8) [89.2 - 96.9]	24 (92.3) [74.9 - 99.1]	63 (92.6) [83.7 - 97.6]	31 (88.6) [73.3 - 96.8]
No	11 (6.2)	2 (7.7)	5 (7.4)	4 (11.4)
I don't know	0	0	0	0
9e: Chronic non-cancer pain				
Yes	57 (32.0)	13 (50.0)	19 (27.9)	17 (48.6)

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
No[2]	121 (68.0) [60.6 - 74.8]	13 (50.0) [29.9 - 70.1]	47 (69.1) [56.7 - 79.8]	17 (48.6) [31.4 - 66.0]
I don't know	0	0	2 (2.9)	1 (2.9)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	17 (9.6)	2 (7.7)	5 (7.4)	1 (2.9)
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.[2]	126 (70.8) [63.5 - 77.3]	19 (73.1) [52.2 - 88.4]	52 (76.5) [64.6 - 85.9]	28 (80.0) [63.1 - 91.6]

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
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.	12 (6.7)	2 (7.7)	4 (5.9)	0
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	8 (4.5)	2 (7.7)	6 (8.8)	3 (8.6)
I don't know	15 (8.4)	1 (3.8)	1 (1.5)	3 (8.6)
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.				
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.				
True[2]	166 (93.3) [88.5 - 96.5]	26 (100.0) [86.8 - 100.0]	62 (91.2) [81.8 - 96.7]	34 (97.1) [85.1 - 99.9]
False	10 (5.6)	0	1 (1.5)	1 (2.9)

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
I don't know	2 (1.1)	0	5 (7.4)	0
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.				
True	39 (21.9)	8 (30.8)	14 (20.6)	3 (8.6)
False[2]	129 (72.5) [65.3 - 78.9]	17 (65.4) [44.3 - 82.8]	49 (72.1) [59.9 - 82.3]	29 (82.9) [66.4 - 93.4]
I don't know	10 (5.6)	1 (3.8)	5 (7.4)	3 (8.6)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.				
True	8 (19.5)	8 (21.1)	35 (28.7)	24 (22.4)
False[2]	30 (73.2) [57.1 - 85.8]	28 (73.7) [56.9 - 86.6]	79 (64.8) [55.6 - 73.2]	75 (70.1) [60.5 - 78.6]
I don't know	3 (7.3)	2 (5.3)	8 (6.6)	8 (7.5)
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.				
True	5 (12.2)	4 (10.5)	30 (24.6)	23 (21.5)
False[2]	32 (78.0) [62.4 - 89.4]	30 (78.9) [62.7 - 90.4]	85 (69.7) [60.7 - 77.7]	77 (72.0) [62.5 - 80.2]
I don't know	4 (9.8)	4 (10.5)	7 (5.7)	7 (6.5)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
Yes	4 (9.8)	1 (2.6)	14 (11.5)	9 (8.4)
No[2]	37 (90.2) [76.9 - 97.3]	37 (97.4) [86.2 - 99.9]	107 (87.7) [80.5 - 93.0]	97 (90.7) [83.5 - 95.4]

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
I don't know	0	0	1 (0.8)	1 (0.9)
9b: Headache or migraine pain				
Yes	1 (2.4)	3 (7.9)	5 (4.1)	7 (6.5)
No[2]	40 (97.6) [87.1 - 99.9]	35 (92.1) [78.6 - 98.3]	117 (95.9) [90.7 - 98.7]	100 (93.5) [87.0 - 97.3]
I don't know	0	0	0	0
9c: Dental pain				
Yes	0	0	2 (1.6)	3 (2.8)
No[2]	41 (100.0) [91.4 - 100.0]	38 (100.0) [90.7 - 100.0]	120 (98.4) [94.2 - 99.8]	104 (97.2) [92.0 - 99.4]
I don't know	0	0	0	0
9d: Breakthrough pain from cancer				
Yes[2]	36 (87.8) [73.8 - 95.9]	38 (100.0) [90.7 - 100.0]	114 (93.4) [87.5 - 97.1]	98 (91.6) [84.6 - 96.1]
No	5 (12.2)	0	8 (6.6)	9 (8.4)
I don't know	0	0	0	0
9e: Chronic non-cancer pain				
Yes	8 (19.5)	11 (28.9)	41 (33.6)	45 (42.1)

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
No[2]	31 (75.6) [59.7 - 87.6]	27 (71.1) [54.1 - 84.6]	81 (66.4) [57.3 - 74.7]	61 (57.0) [47.1 - 66.5]
I don't know	2 (4.9)	0	0	1 (0.9)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	2 (4.9)	4 (10.5)	11 (9.0)	9 (8.4)
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.[2]	35 (85.4) [70.8 - 94.4]	27 (71.1) [54.1 - 84.6]	90 (73.8) [65.0 - 81.3]	73 (68.2) [58.5 - 76.9]

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
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.	0	3 (7.9)	10 (8.2)	5 (4.7)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	3 (7.3)	2 (5.3)	7 (5.7)	7 (6.5)
I don't know	1 (2.4)	2 (5.3)	4 (3.3)	13 (12.1)
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.				
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.				
True[2]	37 (90.2) [76.9 - 97.3]	36 (94.7) [82.3 - 99.4]	115 (94.3) [88.5 - 97.7]	101 (94.4) [88.2 - 97.9]
False	3 (7.3)	1 (2.6)	3 (2.5)	5 (4.7)

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
I don't know	1 (2.4)	1 (2.6)	4 (3.3)	1 (0.9)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.				
True	9 (22.0)	9 (23.7)	26 (21.3)	20 (18.7)
False[2]	30 (73.2) [57.1 - 85.8]	27 (71.1) [54.1 - 84.6]	87 (71.3) [62.4 - 79.1]	80 (74.8) [65.4 - 82.7]
I don't know	2 (4.9)	2 (5.3)	9 (7.4)	7 (6.5)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.					
True	11 (14.3)	43 (27.9)	11 (22.4)	7 (41.2)	3 (23.1)
False[2]	59 (76.6) [65.6 - 85.5]	101 (65.6) [57.5 - 73.0]	36 (73.5) [58.9 - 85.1]	10 (58.8) [32.9 - 81.6]	8 (61.5) [31.6 - 86.1]
I don't know	7 (9.1)	10 (6.5)	2 (4.1)	0	2 (15.4)
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.					
True	11 (14.3)	29 (18.8)	11 (22.4)	5 (29.4)	6 (46.2)
False[2]	61 (79.2) [68.5 - 87.6]	112 (72.7) [65.0 - 79.6]	36 (73.5) [58.9 - 85.1]	12 (70.6) [44.0 - 89.7]	5 (38.5) [13.9 - 68.4]
I don't know	5 (6.5)	13 (8.4)	2 (4.1)	0	2 (15.4)
Question 9: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.					
9a: Acute or postoperative pain					
Yes	5 (6.5)	12 (7.8)	8 (16.3)	2 (11.8)	1 (7.7)

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
No[2]	72 (93.5) [85.5 - 97.9]	141 (91.6) [86.0 - 95.4]	40 (81.6) [68.0 - 91.2]	15 (88.2) [63.6 - 98.5]	12 (92.3) [64.0 - 99.8]
I don't know	0	1 (0.6)	1 (2.0)	0	0
9b: Headache or migraine pain					
Yes	0	8 (5.2)	6 (12.2)	2 (11.8)	0
No[2]	77 (100.0) [95.3 - 100.0]	146 (94.8) [90.0 - 97.7]	43 (87.8) [75.2 - 95.4]	15 (88.2) [63.6 - 98.5]	13 (100.0) [75.3 - 100.0]
I don't know	0	0	0	0	0
9c: Dental pain					
Yes	0	1 (0.6)	2 (4.1)	2 (11.8)	0
No[2]	77 (100.0) [95.3 - 100.0]	153 (99.4) [96.4 - 100.0]	47 (95.9) [86.0 - 99.5]	15 (88.2) [63.6 - 98.5]	13 (100.0) [75.3 - 100.0]
I don't know	0	0	0	0	0
9d: Breakthrough pain from cancer					
Yes[2]	68 (88.3) [79.0 - 94.5]	144 (93.5) [88.4 - 96.8]	47 (95.9) [86.0 - 99.5]	16 (94.1) [71.3 - 99.9]	13 (100.0) [75.3 - 100.0]
No	9 (11.7)	10 (6.5)	2 (4.1)	1 (5.9)	0

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
I don't know	0	0	0	0	0
9e: Chronic non-cancer pain					
Yes	13 (16.9)	53 (34.4)	27 (55.1)	10 (58.8)	3 (23.1)
No[2]	64 (83.1) [72.9 - 90.7]	99 (64.3) [56.2 - 71.8]	22 (44.9) [30.7 - 59.8]	7 (41.2) [18.4 - 67.1]	9 (69.2) [38.6 - 90.9]
I don't know	0	2 (1.3)	0	0	1 (7.7)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.					
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	4 (5.2)	16 (10.4)	3 (6.1)	2 (11.8)	1 (7.7)

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
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.[2]	60 (77.9) [67.0 - 86.6]	107 (69.5) [61.6 - 76.6]	40 (81.6) [68.0 - 91.2]	11 (64.7) [38.3 - 85.8]	9 (69.2) [38.6 - 90.9]
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.	2 (2.6)	7 (4.5)	4 (8.2)	3 (17.6)	2 (15.4)

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	6 (7.8)	11 (7.1)	2 (4.1)	0	0
I don't know	5 (6.5)	13 (8.4)	0	1 (5.9)	1 (7.7)
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.					
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.					
True[2]	70 (90.9) [82.2 - 96.3]	145 (94.2) [89.2 - 97.3]	48 (98.0) [89.1 - 99.9]	17 (100.0) [80.5 - 100.0]	11 (84.6) [54.6 - 98.1]
False	5 (6.5)	5 (3.2)	1 (2.0)	0	1 (7.7)
I don't know	2 (2.6)	4 (2.6)	0	0	1 (7.7)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.					
True	15 (19.5)	28 (18.2)	13 (26.5)	4 (23.5)	4 (30.8)

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
False[2]	52 (67.5) [55.9 - 77.8]	121 (78.6) [71.2 - 84.8]	31 (63.3) [48.3 - 76.6]	13 (76.5) [50.1 - 93.2]	9 (69.2) [38.6 - 90.9]
I don't know	10 (13.0)	5 (3.2)	5 (10.2)	0	0

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Key Risk Message #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® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.

Correct Responses	Prescribers (N=310) n (%) [95% CI][1]
0 correct responses	0
1 correct response	0
2 correct responses	1 (0.3)
3 correct responses	3 (1.0)
4 correct responses	5 (1.6)
5 correct responses	12 (3.9)
6 correct responses	29 (9.4)
7 correct responses	39 (12.6)
8 correct responses	57 (18.4)
9 correct responses	82 (26.5)
10 correct responses	82 (26.5) [21.6 - 31.7]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Prescribers (N=310) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[2]	306 (98.7) [96.7 - 99.6]
False	2 (0.6)
I don't know	2 (0.6)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[2]	262 (84.5) [80.0 - 88.4]
No	28 (9.0)
I don't know	20 (6.5)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[2]	306 (98.7) [96.7 - 99.6]
No	4 (1.3)
I don't know	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[2]	292 (94.2) [91.0 - 96.5]
False	12 (3.9)
I don't know	6 (1.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.2: Responses to Questions Linked to Key Risk Message #3 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True[2]	176 (98.9) [96.0 - 99.9]	26 (100.0) [86.8 - 100.0]	66 (97.1) [89.8 - 99.6]	35 (100.0) [90.0 - 100.0]
False	1 (0.6)	0	1 (1.5)	0
I don't know	1 (0.6)	0	1 (1.5)	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes[2]	149 (83.7) [77.4 - 88.8]	22 (84.6) [65.1 - 95.6]	57 (83.8) [72.9 - 91.6]	32 (91.4) [76.9 - 98.2]
No	17 (9.6)	3 (11.5)	6 (8.8)	2 (5.7)
I don't know	12 (6.7)	1 (3.8)	5 (7.4)	1 (2.9)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes[2]	176 (98.9) [96.0 - 99.9]	26 (100.0) [86.8 - 100.0]	66 (97.1) [89.8 - 99.6]	35 (100.0) [90.0 - 100.0]
No	2 (1.1)	0	2 (2.9)	0
I don't know	0	0	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				

Table 9.1.2: Responses to Questions Linked to Key Risk Message #3 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True[2]	166 (93.3) [88.5 - 96.5]	26 (100.0) [86.8 - 100.0]	62 (91.2) [81.8 - 96.7]	35 (100.0) [90.0 - 100.0]
False	8 (4.5)	0	4 (5.9)	0
I don't know	4 (2.2)	0	2 (2.9)	0

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.4: Responses to Questions Linked to Key Risk Message #3 by Time Practicing Medicine - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True[2]	41 (100.0) [91.4 - 100.0]	37 (97.4) [86.2 - 99.9]	121 (99.2) [95.5 - 100.0]	105 (98.1) [93.4 - 99.8]
False	0	0	1 (0.8)	1 (0.9)
I don't know	0	1 (2.6)	0	1 (0.9)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes[2]	35 (85.4) [70.8 - 94.4]	34 (89.5) [75.2 - 97.1]	104 (85.2) [77.7 - 91.0]	87 (81.3) [72.6 - 88.2]
No	4 (9.8)	4 (10.5)	9 (7.4)	11 (10.3)
I don't know	2 (4.9)	0	9 (7.4)	9 (8.4)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes[2]	40 (97.6) [87.1 - 99.9]	38 (100.0) [90.7 - 100.0]	120 (98.4) [94.2 - 99.8]	106 (99.1) [94.9 - 100.0]
No	1 (2.4)	0	2 (1.6)	1 (0.9)
I don't know	0	0	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				

Table 9.1.4: Responses to Questions Linked to Key Risk Message #3 by Time Practicing Medicine - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True[2]	38 (92.7) [80.1 - 98.5]	34 (89.5) [75.2 - 97.1]	115 (94.3) [88.5 - 97.7]	103 (96.3) [90.7 - 99.0]
False	2 (4.9)	2 (5.3)	5 (4.1)	3 (2.8)
I don't know	1 (2.4)	2 (5.3)	2 (1.6)	1 (0.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.5: Responses to Questions Linked to Key Risk Message #3 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.					
True[2]	76 (98.7) [93.0 - 100.0]	152 (98.7) [95.4 - 99.8]	48 (98.0) [89.1 - 99.9]	17 (100.0) [80.5 - 100.0]	13 (100.0) [75.3 - 100.0]
False	0	1 (0.6)	1 (2.0)	0	0
I don't know	1 (1.3)	1 (0.6)	0	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.					
8a: A personal history of psychiatric illness					
Yes[2]	67 (87.0) [77.4 - 93.6]	130 (84.4) [77.7 - 89.8]	39 (79.6) [65.7 - 89.8]	16 (94.1) [71.3 - 99.9]	10 (76.9) [46.2 - 95.0]
No	5 (6.5)	16 (10.4)	5 (10.2)	1 (5.9)	1 (7.7)
I don't know	5 (6.5)	8 (5.2)	5 (10.2)	0	2 (15.4)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse					
Yes[2]	77 (100.0) [95.3 - 100.0]	153 (99.4) [96.4 - 100.0]	47 (95.9) [86.0 - 99.5]	17 (100.0) [80.5 - 100.0]	12 (92.3) [64.0 - 99.8]
No	0	1 (0.6)	2 (4.1)	0	1 (7.7)
I don't know	0	0	0	0	0

Table 9.1.5: Responses to Questions Linked to Key Risk Message #3 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.					
True[2]	72 (93.5) [85.5 - 97.9]	145 (94.2) [89.2 - 97.3]	47 (95.9) [86.0 - 99.5]	17 (100.0) [80.5 - 100.0]	11 (84.6) [54.6 - 98.1]
False	3 (3.9)	7 (4.5)	1 (2.0)	0	1 (7.7)
I don't know	2 (2.6)	2 (1.3)	1 (2.0)	0	1 (7.7)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Key Risk Message #3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

Correct Responses	Prescribers (N=310) n (%) [95% CI][1]
0 correct responses	1 (0.3)
1 correct response	0
2 correct responses	6 (1.9)
3 correct responses	58 (18.7)
4 correct responses	245 (79.0) [74.1 - 83.4]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 10.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Prescribers (N=310) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	13 (4.2)
False[2]	287 (92.6) [89.1 - 95.2]
I don't know	10 (3.2)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[2]	296 (95.5) [92.5 - 97.5]
False	6 (1.9)
I don't know	8 (2.6)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[2]	279 (90.0) [86.1 - 93.1]
False	21 (6.8)
I don't know	10 (3.2)
Question 16: 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. According to the labeling, how should the prescriber proceed? Please select one option.	
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	3 (1.0)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	240 (77.4) [72.4 - 82.0]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	22 (7.1)
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.	33 (10.6)

Table 10.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Prescribers (N=310) n (%) [95% CI][1]
I don't know.	12 (3.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.2: Responses to Questions Linked to Key Risk Message #4 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
12b: TIRF medicines are interchangeable with each other regardless of route of administration.				
True	11 (6.2)	0	1 (1.5)	1 (2.9)
False[2]	162 (91.0) [85.8 - 94.8]	25 (96.2) [80.4 - 99.9]	64 (94.1) [85.6 - 98.4]	33 (94.3) [80.8 - 99.3]
I don't know	5 (2.8)	1 (3.8)	3 (4.4)	1 (2.9)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True[2]	169 (94.9) [90.6 - 97.7]	25 (96.2) [80.4 - 99.9]	66 (97.1) [89.8 - 99.6]	33 (94.3) [80.8 - 99.3]
False	4 (2.2)	1 (3.8)	1 (1.5)	0
I don't know	5 (2.8)	0	1 (1.5)	2 (5.7)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True[2]	165 (92.7) [87.8 - 96.1]	23 (88.5) [69.8 - 97.6]	60 (88.2) [78.1 - 94.8]	28 (80.0) [63.1 - 91.6]
False	9 (5.1)	2 (7.7)	5 (7.4)	5 (14.3)
I don't know	4 (2.2)	1 (3.8)	3 (4.4)	2 (5.7)
Question 16: 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. According to the labeling, how should the prescriber proceed? Please select one option.				

Table 10.1.2: Responses to Questions Linked to Key Risk Message #4 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	1 (0.6)	1 (3.8)	0	1 (2.9)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	137 (77.0) [70.1 - 82.9]	21 (80.8) [60.6 - 93.4]	52 (76.5) [64.6 - 85.9]	27 (77.1) [59.9 - 89.6]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	12 (6.7)	0	7 (10.3)	3 (8.6)

Table 10.1.2: Responses to Questions Linked to Key Risk Message #4 by Medical Degree of Respondents - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Medical Degree of Respondents			
	MD (N=178) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=68) n (%) [95% CI][1]	Physician Assistant (N=35) n (%) [95% CI][1]
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.	20 (11.2)	4 (15.4)	6 (8.8)	3 (8.6)
I don't know.	8 (4.5)	0	3 (4.4)	1 (2.9)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.4: Responses to Questions Linked to Key Risk Message #4 by Time Practicing Medicine - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
12b: TIRF medicines are interchangeable with each other regardless of route of administration.				
True	1 (2.4)	0	7 (5.7)	5 (4.7)
False[2]	38 (92.7) [80.1 - 98.5]	38 (100.0) [90.7 - 100.0]	108 (88.5) [81.5 - 93.6]	101 (94.4) [88.2 - 97.9]
I don't know	2 (4.9)	0	7 (5.7)	1 (0.9)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True[2]	39 (95.1) [83.5 - 99.4]	36 (94.7) [82.3 - 99.4]	115 (94.3) [88.5 - 97.7]	104 (97.2) [92.0 - 99.4]
False	2 (4.9)	0	2 (1.6)	2 (1.9)
I don't know	0	2 (5.3)	5 (4.1)	1 (0.9)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True[2]	36 (87.8) [73.8 - 95.9]	35 (92.1) [78.6 - 98.3]	110 (90.2) [83.4 - 94.8]	96 (89.7) [82.3 - 94.8]
False	3 (7.3)	3 (7.9)	8 (6.6)	7 (6.5)
I don't know	2 (4.9)	0	4 (3.3)	4 (3.7)
Question 16: 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. According to the labeling, how should the prescriber proceed? Please select one option.				

Table 10.1.4: Responses to Questions Linked to Key Risk Message #4 by Time Practicing Medicine - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	1 (2.4)	0	0	2 (1.9)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	33 (80.5) [65.1 - 91.2]	29 (76.3) [59.8 - 88.6]	97 (79.5) [71.3 - 86.3]	79 (73.8) [64.4 - 81.9]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	0	2 (5.3)	9 (7.4)	11 (10.3)

Table 10.1.4: Responses to Questions Linked to Key Risk Message #4 by Time Practicing Medicine - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Time Practicing Medicine			
	Less than 3 years (N=41) n (%) [95% CI][1]	3 to 5 years (N=38) n (%) [95% CI][1]	6 to 15 years (N=122) n (%) [95% CI][1]	More than 15 years (N=107) n (%) [95% CI][1]
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.	6 (14.6)	6 (15.8)	13 (10.7)	8 (7.5)
I don't know.	1 (2.4)	1 (2.6)	3 (2.5)	7 (6.5)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.5: Responses to Questions Linked to Key Risk Message #4 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
12b: TIRF medicines are interchangeable with each other regardless of route of administration.					
True	1 (1.3)	6 (3.9)	2 (4.1)	3 (17.6)	1 (7.7)
False[2]	76 (98.7) [93.0 - 100.0]	140 (90.9) [85.2 - 94.9]	46 (93.9) [83.1 - 98.7]	13 (76.5) [50.1 - 93.2]	12 (92.3) [64.0 - 99.8]
I don't know	0	8 (5.2)	1 (2.0)	1 (5.9)	0
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.					
True[2]	75 (97.4) [90.9 - 99.7]	147 (95.5) [90.9 - 98.2]	46 (93.9) [83.1 - 98.7]	16 (94.1) [71.3 - 99.9]	12 (92.3) [64.0 - 99.8]
False	1 (1.3)	3 (1.9)	1 (2.0)	0	1 (7.7)
I don't know	1 (1.3)	4 (2.6)	2 (4.1)	1 (5.9)	0
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.					
True[2]	69 (89.6) [80.6 - 95.4]	139 (90.3) [84.4 - 94.4]	45 (91.8) [80.4 - 97.7]	14 (82.4) [56.6 - 96.2]	12 (92.3) [64.0 - 99.8]
False	7 (9.1)	7 (4.5)	4 (8.2)	2 (11.8)	1 (7.7)
I don't know	1 (1.3)	8 (5.2)	0	1 (5.9)	0

Table 10.1.5: Responses to Questions Linked to Key Risk Message #4 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Question 16: 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. According to the labeling, how should the prescriber proceed? Please select one option.					
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	2 (1.3)	0	0	1 (7.7)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	63 (81.8) [71.4 - 89.7]	120 (77.9) [70.5 - 84.2]	42 (85.7) [72.8 - 94.1]	10 (58.8) [32.9 - 81.6]	5 (38.5) [13.9 - 68.4]

Table 10.1.5: Responses to Questions Linked to Key Risk Message #4 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=77) n (%) [95% CI][1]	1 - 2 times per month (N=154) n (%) [95% CI][1]	3 - 5 times per month (N=49) n (%) [95% CI][1]	More than 5 times per month (N=17) n (%) [95% CI][1]	I don't remember (N=13) n (%) [95% CI][1]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	2 (2.6)	11 (7.1)	3 (6.1)	4 (23.5)	2 (15.4)
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.	8 (10.4)	17 (11.0)	4 (8.2)	1 (5.9)	3 (23.1)
I don't know.	4 (5.2)	4 (2.6)	0	2 (11.8)	2 (15.4)

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Key Risk Message #4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

Correct Responses	Prescribers (N=310) n (%) [95% CI][1]
0 correct responses	3 (1.0)
1 correct response	8 (2.6)
2 correct responses	13 (4.2)
3 correct responses	76 (24.5)
4 correct responses	210 (67.7) [62.2 - 72.9]

[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.

Table 11: Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106)[1] n (%)
Question 10: For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?	
Total Number of Responses[2]	214
Back Pain	34 (32.1)
Cancer Pain	24 (22.6)
Neuropathic Pain	23 (21.7)
Post-Operative Pain	20 (18.9)
Chronic Pain	19 (17.9)
Joint Pain	11 (10.4)
Reflex Sympathetic Dystrophy	10 (9.4)
Complex Regional Pain Syndrome	8 (7.5)
Spinal Pain	8 (7.5)
Neck Pain	5 (4.7)
Abdominal Pain	4 (3.8)
Muscoskeletal Pain	4 (3.8)
Sickle Cell	4 (3.8)
Gastrointestinal Pain	3 (2.8)
Migraines	3 (2.8)
Palliative Care	3 (2.8)
Pancreatitis	3 (2.8)
Spinal Stenosis	3 (2.8)
Breakthrough Pain	2 (1.9)
Oral Pain	2 (1.9)
Wound Pain	2 (1.9)
Allergic to morphine and dilaudid	1 (0.9)
Chronic wounds	1 (0.9)
Intestinal absorption problems	1 (0.9)
Ischemic Peripheral Vascular Disease	1 (0.9)

Table 11: Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106)[1] n (%)
Multiple Sclerosis	1 (0.9)
Neuropathy	1 (0.9)
Radiculopathy	1 (0.9)
Somatic pain	1 (0.9)
Trauma Pain	1 (0.9)
Wound Care	1 (0.9)
Other[3]	9 (8.5)

[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Chronic Non-Cancer Pain-"Yes"*) and were subsequently presented Question 10 and Question 11.
[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.
[3] Other includes responses that were not categorized or responses that did not include a medical condition.

Table 12: Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106)[1] n (%)
Question 11: Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?	
Total Number of Responses[2]	169
Efficacy	38 (35.8)
Fast Acting	36 (34.0)
Other Types of Medications have Failed	30 (28.3)
Breakthrough Pain	15 (14.2)
Ease of Use	5 (4.7)
Preferred Route of Administration	5 (4.7)
Abuse/Diversion Deterrence	4 (3.8)
Long Duration of Action	4 (3.8)
Opioid Rotation	3 (2.8)
Potency	3 (2.8)
Quality of Life	3 (2.8)
Insurance	2 (1.9)
Pain Management	2 (1.9)
Compliance	1 (0.9)
Consistent Control	1 (0.9)
Less Toxicities Compared to Other Opioids	1 (0.9)
Patient Cannot Tolerate Other Options	1 (0.9)
Practice Preference	1 (0.9)
Preferred route of administration	1 (0.9)
Prescribed by another physician before becoming a patient	1 (0.9)
Severe Pain	1 (0.9)

Table 12: Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=106)[1] n (%)
Other[3]	11 (10.4)

[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Chronic Non-Cancer Pain-"Yes"*) and were subsequently presented Question 10 and Question 11.
[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.
[3] Other includes responses that were not categorized or responses that did not include a medical condition.

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-000763	1) Malignancy related 2) Peripheral neuropathy
0004-001022	100
0004-001315	Arthritis, Refractory or Chronic Neuropathy/Neuralgia responsive to opiates, Degenerative Disc Disease, Chronic wounds or complications, Dental complications or Mucositis, and Metastatic Disease
0004-001213	Arthritis, migraines, neuropathic pain
0004-001225	Back pain. neuropathy
0004-001305	Besides cancer pain, I have used TIRF meds for avascular necrosis with joint destruction when regular opioids were required.
0004-001178	Breakthrough pain in cancer patients, Chronic neuropathic pain and failed back surgery syndrome due to nerve damage/irritation in patients that cannot swallow due to other GI/craniofacial medical conditions.
0004-001197	Burning mouth syndrome, short gut syndrome
0004-000850	CANCER, COMPRESSION FRACTURES
0004-001299	CHRONIC PAIN
0004-001215	CHRONIC SPINAL RELATED PAIN SYNDROMES
0004-000773	CRPS, severe nonresponsive to other treatment back or neck pain
0004-000578	Cancer pain
0004-000454	Cancer patients
0004-001102	Cancer related pain only
0004-000886	Cancer related, sickle cell, muscoskeletal, neurologic.
0004-001050	Cancer, spine diseases, severe rheumatologic disease
0004-000852	Chronic back pain Chronic pain secondary to ischemic PVD/non-healing leg wounds
0004-001079	Chronic pain from cancer
0004-001182	Chronic pain syndrome
0004-001075	Chronic pain taking long acting med who need breakthrougn med
0004-000558	Chronic pain when there are severe discrete episodes of debilitating breakthrough pain
0004-001161	Chronic pain where an oral medication cannot be tolerated.
0004-001084	Chronic post surgical (abdominal, lumbar, orthopedic) pain refractory to other narcotics, Advanced chronic pancreatitis pain.
0004-001239	Chronic regional pain syndrome; advanced degenerative joint disease; medullary sponge kidney.

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001176	Chronic sacral pain, chronic back pain that surgery has not helped and patient can't get any relief during BM
0004-001130	Complex Regional Pain Syndrom
0004-000383	Complex regional pain syndrome. Cancer patients.
0004-001290	FAILED BACK SYNDROME , NON OPERATIVE CERVICAL OR LUMBAR DISC DISEASE
0004-000495	Failed Back Syndrome General chronic pain syndrome Severe neck pain Complex Regional pain syndrome Any Peripheral Neuropathy
0004-000637	Failed Back Syndrome, Postlaminectomy Syndrome, RSD
0004-001131	Failed Surgical Syndrome, Peripheral Neuropathy
0004-001096	Failed back surgery pain, CRPS
0004-001077	Failed back syndrome, Chronic low back and neck pain, RSD
0004-000391	Failed back syndrome; chronic pelvic pain with dyspareunia;
0004-001073	I only have one pt with significant back pain and an extensive operative history-otherwise it is only used for cancer pts
0004-000851	Intractable back pain in patients with high opioid tolerance
0004-001105	Life limiting illnesses such as COPD, CHF, etc. Those that are progressive, irreversible and terminal. As a palliative care physician I utilize TIRF medicine to manage negative symptoms of conditions that have a chronic pain(as well as dyspnea) component. I do not treat 'chronic pain' patients but all conditions I do see have or have the potential to have a pain component.
0004-001177	MIgraines
0004-001237	PATIENTS WHO HAVE TRIED ALL OTHER INTERVENTIONAL MEDICATIONS
0004-001149	Patient who need round the clock medicaiton w/o frequent dosing.
0004-001151	Patients with chronic wounds prior to wound care
0004-001180	Post thalamic stroke pain syndrome
0004-001056	Post-lami syndrome
0004-000822	Post-laminectomy Pain Syndrome, Complex Regional Pain Syndrome.
0004-000926	Postlaminectomy syndrome; severe neuropathy; chronic severe trauma patients-paraplegic,etc.
0004-001044	Primarily Cancer Pain
0004-001071	Profound end-stage RA

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-000765	RSD
0004-001157	RSD
0004-001194	Refractory Neuropathic severe episodic pain
0004-001080	SPINAL STENOSIS, ARTHRITIS, FIBRO
0004-001141	Severe Musculoskeletal and Neuropathic-type pain conditions.
0004-000667	Severe joint pains secondary to avascular necrosis, joint replacements, or severe arthritic conditions.
0004-000799	Severe, unremitting, rapid onset neuropathic pain not controlled by long and other short-acting opioids, and which are unresponsive to non-opioid medications, a cause is known, and for which other surgical/ injection treatment options have failed.
0004-001304	Spine related, radiculopathy, neuropathy
0004-001170	TRIGEMINAL NEURALGIA
0004-001027	Uncontrolled with traditional short acting opioids due to speed of onset
0004-000920	We have a patient with chronic abdominal pain, chronic pain after ovarian cancer and a patient with uncontrollable pain after back surgery
0004-000787	abdominal pain due to chrons
0004-001214	back pain
0004-000896	cancer
0004-001206	cancer associated pain, chronic arthritis
0004-001106	cancer pain syndromes, mainly
0004-000628	cancer pain, chronic pain syndromes(low back, spondylosis, ect) not amenable to other opioid regimens
0004-000833	cancer pain, spinal cord injury pain. nerve pain, muscularskeletal pain
0004-000432	cancer, RSD, some types of neuropathic pain
0004-000444	cancer,chronic back pain, migraine
0004-000485	ch. pancreatitis
0004-000433	chronic back pain
0004-000480	chronic back pain, chronic joint pain
0004-001279	chronic cancer related pain
0004-001257	chronic intractable head/facial pain after MVA with facial implants.
0004-000767	chronic low back pains

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001162	chronic neuropathic pain
0004-001128	chronic pain due to injury, oa, lumbar ddd
0004-000761	chronic pain that is treatment related and not controlled by other means of medication.
0004-001168	chronic uncontrolled pain, especially abdominal pain and spine pain conditions
0004-000514	chronic with acute exacerbations
0004-000498	chrons dz post chemo neuropathy post xrt neuropathy
0004-001053	end stage life limiting disease in patients who are on hospice, such as advanced arthritis, end stage neurologic disease
0004-001112	failed back syndrome
0004-001199	intolerant to oral opioids due to intestinal absorption problems, cancer pain
0004-000396	low back pain
0004-000923	low back, post lami syndrome, resistant RSD, Other chronic pain conditions
0004-001094	lower back pain, neck pain, rsd, ms rheumatoid arthritis
0004-000477	multiple sclerosis neuropathic pain, diabetic polyneuropathy, cervical/lumbar stenosis, failed neck/back syndromes, cancer pain (multiple types)
0004-000448	neuropathic pain
0004-000417	non-responsive neuralgia's, crippling CRPS
0004-000473	pancreatitis abdominal pain severe failed back syndrome
0004-001078	patients who have allergies to dilaudid and morphine and patients on opiates for dressing changes/wound care.
0004-000402	post laminectomy syndrome
0004-000759	post laminectomy syndrome, chronic radiculopathy, spondylolisthesis, foraminal stenosis, sponydylosis
0004-001072	post laminectomy syndromes, severe spinal stenosis, severe total body pain syndromes
0004-001200	primarily chronic spinal or musculoskeletal pain - may or may not be related to their underlying cancer diagnosis
0004-000569	rare patients for whom conventional IR meds are ineffective
0004-001292	scoliosis, neuropathic leg pain
0004-001145	sever chronic Pain from sever arthritis or back surgery if they are opioid tolerant
0004-001068	severe cases of RSD that are not responsive to DRG blocks, and around the clock opiod therapy

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-000435	sickle cell patients, chronic regional pain syndrome
0004-000916	sickle cell, abdominal pain
0004-001089	somatic or neuropathic both work
0004-001081	spinal myelopathic pain sickle cell crisis
0004-001308	spinal stenosis, severe joint OA, chronic pain s/p multi trauma
0004-000555	trigeminal neuralgia
0004-001098	unspecified chronic pain uncontrolled by all other means

Note: Question 10 is only asked if Question 9e is answered "Yes".

Listing 1.2: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Incomplete Surveys

Survey Form ID	Verbatim Responses
0004-001063	CRPS
0004-001228	Cancer, Neuropathic pain, Chronic intractable pain
0004-001016	Chronic abdominal pain related to multiple surgeries, surgical complications or complex GI issues
0004-001259	Failed back surgery. Lumbar radiculopathy
0004-000361	LBP SC anemia
0004-001003	Usually use fentanyl patch for chronic back or neck pain due to failed surgery.
0004-001258	breakthough pain that is fast acting to allow for transfers from bed to wheelchair on a PRN basis
0004-000324	chronic low back pain
0004-000428	sickle cell anemia
0004-001217	spinal related pain, joint pain,

Note: Question 10 is only asked if Question 9e is answered "Yes".

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001237	ABUSE DETERRENT
0004-001194	All else has failed and need the acute onset
0004-000852	Around the clock therapy is more advantageous for chronic pain than frequent dosing of short acting opioids. Less risk of patient abusing patch vs access to multiple pills.
0004-001299	BREAKTHROUGH
0004-001213	Because a non opioid will not work.
0004-001182	Because nothing else is working.
0004-000667	Because patient's pain is not controlled with long-acting and short-acting opiates.
0004-001075	Because they still work a bit
0004-001151	Because they work quickly and are very effective
0004-001199	Better control of pain/functionality usually in cancer patients that have tried other opioids unsucessfully
0004-001315	Breakthrough pain, easier application, patients with Nausea/Vomiting, or difficulty with PO routes of medication
0004-001197	Cant take oral or orals not potent enough
0004-000765	Consistent round the clock pain control
0004-001105	Ease of use, efficacy in most patients, ability to titrate rapidly and safely.
0004-000578	Easy administration and rapid onset
0004-001096	Efficacy, compliance
0004-001257	Failed all other breakthrough meds previously
0004-000851	Failed multiple other breakthrough opiate analgesics,modalities of pain relief
0004-000391	Failed other opioid agents and still have pain scores greater than 7/10.TIRF medicine allows them to function.
0004-001068	Failure of the the conventional medications and procedures to provide relief
0004-001141	Fast onset of action. Catches BTP episode as quickly as possible allowing greater chance of bringing under control.
0004-001130	Fastest relief in acute breakthrough pain
0004-000822	For episodes of acute exacerbation from activity.
0004-001168	For immediate control of sudden acute pain flares and to better control the peaks of pain
0004-000761	I do so rarely in patients with non tolerable pain not managed by other means

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001098	I only have one patient treated with a TIRF medication and he was previously on the medication before coming to my clinic. He has a complicated history and it is the only medication that controls his chronic pain
0004-001071	I prefer to minimize the number of opioid molecules used in any pain mgt regiment. I only prescribe TIRF product to pts that are already on fentanyl at least 100mcg/hr
0004-001102	I use this product when we are looking for management of acute, pain flares in cancer related pain for patients who are opioid tolerant. I use it there current BTD are not covering severe pain crisis and goal is to keep pt out of the ER setting
0004-001050	If needed for adequate pain control
0004-000558	If the pain comes on quickly, These medications bring the quickest relief
0004-000773	It allows fast effective relief for severe episodes of BTP
0004-001180	It has been effective and the patient entered my care from another provider who had initiated TIRF treatment
0004-001131	It has provided them beneficial control of breakthrough pain when needed.
0004-000759	It helps to minimize the possibility of pill abuse and also helps those who do not want to have pills in their home due to fear of theft
0004-001215	LONG DURATION OF ACTION
0004-000799	Last resort
0004-000886	Less toxicities compared to oral morphine or oxycodone. Better pain relief compared to other short acting pain medications.
0004-001149	Long acting forms and the fact that I can use a patch and avoid taking frequent doses orally.
0004-001170	Many non TIRF medications were tried first with little success in pain control and functional stability
0004-000763	Need for rapid onset analgesia with short duration.
0004-001077	Nothing has worked that well. Opioid rotation
0004-001308	Only if other meds have failed or opiate genotype suggests abnormal metabolism
0004-001161	Oral medication is not an option.
0004-001225	Other meds haven't worked
0004-001073	Pt did not respond to other opioid therapies including intrathecal pump placement
0004-001304	Quick Onset for breakthrough or activity induced pain
0004-001079	Quick acting for breakthrough pain
0004-001162	Rapid onset of action

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001290	TO AVOID MULTIPLE OPIOID MEDICATION
0004-000850	TO GIVE IMMEDIATE BREAK THROUGH PAIN RELIEF
0004-000495	The reason being I have lots of patients by the time they have been referred to me they have tried lots of other of medicines, and none seem to be working. Second reason is if they are already on the patch and that seems to be working, but they still need something for breakthrough pain this will be a good complimentary.
0004-000402	They are already on a long acting opioid, typically fentanyl, and need a fast acting breakthrough agent
0004-001176	They have a sudden pain with BM and the TIRF medication can help in only a few minutes as apposed to 30 - 45 min The have severe pain with BM's and they need the help as soon as they feel that they are going to have a BM
0004-000637	They have failed other opiate meds
0004-000920	They have tried and failed every other break through pain medication and the pain could not be controlled any other way.
0004-000383	To improve function and quality of life.
0004-001305	Tolerating opioids and clearly benefitting up to a certain dose.
0004-001080	USE THEM AS PART OF OPIOID ROTATION
0004-001214	Well efficacy
0004-001044	When short acting and fast onset is necessary. Patients wanting a clear sensorium as much as possible.
0004-000896	addresses pain well, titratable, covered by insurance
0004-001239	augment pain management.
0004-000396	cannot tolerate fentanyl patches
0004-001084	dor pain that is refractory to higher doses of conventional narcotics.
0004-000555	due to severe pain
0004-001027	due to ultra fast time of onset
0004-000444	effectiveness
0004-000916	efficacy
0004-000454	efficacy lack of other options
0004-000448	efficacy of fentanyl product
0004-000628	fast acting relief. Also they must fail other IR med such as norco and percocet.
0004-001094	fast acting, and potent

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001177	fast acting, failed other medications
0004-001072	fast onset, reliable medication
0004-001022	good
0004-001056	good response to pain relief
0004-000432	immediate onset of relief. History of opioid tolerance and benefit of opioid rotation
0004-000480	in order to provide immediate release of the medication with a short duration of start of effect
0004-000433	it works and lasts them a little longer.
0004-001112	its effectiveness
0004-000435	last resort and works quickly
0004-001200	need for fast acting medication or an intolerance of other available agents
0004-000477	need for more potent effect to cover their persistent pain
0004-001106	need for ultra-fast acting pain relief
0004-001081	neuropathic pain with acute exacerbation is often refractory to slower onset rescue medicines sickle cell crisis pain can be abrupt and refractory to slower acting agents
0004-000787	no other medications help quick enough for the episodic pain
0004-001053	non functioning GI tract,or to avoid high pill burden, or in cases of possible med diversion, or in cases where patient and care giver cannot follow a schedule of oral meds.
0004-000417	only use if patient has sudden onset short-lasting debilitating pain
0004-001078	onset of action
0004-001128	pain relief
0004-001279	provides better pain relief
0004-000767	pt has been on chronic opioid therapy with diminishing effects
0004-000485	pt was on before he saw us. no longer of tirf med 2/2 lack of insurance coverage for med.
0004-000473	quick on set of relief and good relief is given when used (patient specific, of course)
0004-001157	quick onset
0004-000514	quick onset, effective
0004-001206	quick onset, effective pain relief, ease of administration and absorption especially in cancer patients with decreased GI absorption or nausea/vomiting from chemo, ability for patient to quickly titrate to optimal dose

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0004-001178	rapid onset and offset which is ideal for true breakthrough or daily flares
0004-000569	see prev answer
0004-001292	sseverity
0004-000498	they have positive therapuetic benefit and have failed other conservative measures.
0004-001145	to help in breakthrough pain addition to long pain meds
0004-000833	to try to decrease baseline pain in order to decrease more short acting medication usage
0004-001089	we need to use the best drug available to control the pain
0004-000926	when they have failed other meds, to prevent visits to ER and to improve quality of life for the patient
0004-000923	works

Note: Question 11 is only asked if Question 9e is answered "Yes".

Listing 2.2: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?) - Incomplete Surveys

Survey Form ID	Verbatim Responses
0004-001003	Fentanyl patch is harder to abuse also is good in elderly patients who may have kidney issues.
0004-001228	For breakthrough pain
0004-001259	Most are rotated when other pain meds are ineffective
0004-001258	Other immediate release medications have been prescribed in the past and have not worked. Due to my patinets unique disease process and QOL this worked best for her pain.
0004-001063	Patients have tried and failed at other meds before I see them
0004-001016	Usually at the recommendation of the palliative care team or allergies
0004-001217	if a pt is not obtaining adequate relief and function is decreased with up to 4 IR medications/day
0004-000428	patient preference
0004-000361	poor renal function, poor liver function intolerance of others medication with prominent side effect inability to swallow etc
0004-000324	poor response

Note: Question 11 is only asked if Question 9e is answered "Yes".

Listing 3: Listing of Verbatim Responses to Question #26 (Questions about the Medication Guide) - Completed Surveys

Verbatim Responses
Although not applicable to my patient, I would need to refer to the guide re initiating TIRF to any patient already on opiods
Best time period and setting to do initial titration. Home vs. in-office initial up-titration to find effective dose.
Can they use it without a long acting narcotic? All of my patients are on a long acting narcotic.
Guidance on prescribing on individual cases...answered by supervising physician.
How do I prescribe them?
I cannot remember
I work in inpatient oncology. We have been taught by our pharmacy that the use of certain TIRF medications, specifically actiq, is acceptable for inpatient procedure pain control (such as bone marrow aspiration and biopsy) although this seems to be in conflict with the product labeling which specifically contraindicates use for acute operative pain.
What relevant info is contained
Where do I obtain this information?
metabolism with liver enzymes
safe measures to prevent accidental overdose.
where is guideline available?

Listing 4: Listing of Verbatim Responses to Question #37 (What is your medical specialty?) - Completed Surveys

Verbatim Responses
Anesthesia
Family
Family practice
Gastroenterology
HIV and Family Medicine
Hospice and Palliative Care
Hospice and Palliative Med
Hospice and Palliative Medicine
Hospice and Palliative Medicine
Hospice and Palliative Medicine/Pain Management
Internal Medicine
Internal Medicine
Interventional Radiology
Interventional Radiology
Neurology
Neurology
Neurology
Neurology
Neurosurgery
Oncology Palliative Care
PM&R
PM&R
PM&R
Pain and palliative care and rehabilitation
Palliative
Palliative
Palliative Care
Palliative Care
Palliative Care

Listing 4: Listing of Verbatim Responses to Question #37 (What is your medical specialty?) - Completed Surveys

Verbatim Responses
Palliative Care
Palliative Care
Palliative Care
Palliative Care
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine
Palliative Medicine and Palliative Oncology
Palliative care
Palliative care
Physical Medicine & Rehabilitation
Physical Medicine & Rehabilitation
Physical medicine and rehabilitation
Radiation Oncology
Radiation Oncology
anesthesia
hospice and palliative medicine
hospice/pall med
ortho surgery
palliative care
palliative care
palliative care
palliative care

Listing 4: Listing of Verbatim Responses to Question #37 (What is your medical specialty?) - Completed Surveys

Verbatim Responses
palliative care
palliative medicine
palliative medicine
palliative medicine
palliative medicine
pmr
radiation oncology

Listing 5: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
Chronic Low Back Pain	Internet
poor renal function, poor liver function intolerance of others medication with prominent side effect inability to swallow etc	Internet
Complex regional pain syndrome. Cancer patients.	Internet
Failed back syndrome; chronic pelvic pain with dyspareunia;	Internet
low back pain	Internet
post laminectomy syndrome	Internet
non-responsive neuralgia's, crippling CRPS	Internet
sickle cell anemia	Internet
cancer, RSD, some types of neuropathic pain	Internet
chronic back pain	Telephone
sickle cell patients, chronic regional pain syndrome	Internet
cancer,chronic back pain, migraine	Internet
neuropathic pain	Telephone
pancreatitis abdominal pain severe failed back syndrome	Internet
multiple sclerosis neuropathic pain, diabetic polyneuropathy, cervical/lumbar stenosis, failed neck/back syndromes, cancer pain (multiple types)	Internet
chronic back pain, chronic joint pain	Internet
ch. Pancreatitis	Internet
Failed Back Syndrome General chronic pain syndrome Severe neck pain Complex Regional pain syndrome Any Peripheral Neuropathy	Telephone
chrons dz post chemo neuropathy post xrt neuropathy	Internet
cancer pain, chronic pain syndromes(low back, spondylosis, ect) not amenable to other opioid regimens	Internet
Failed Back Syndrome, Postlaminectomy Syndrome, RSD	Internet
Severe joint pains secondary to avascular necrosis, joint replacements, or severe arthritic conditions.	Internet
post laminectomy syndrome, chronic radiculopathy, spondylolisthesis, foraminal stenosis, sponydylosis	Internet
RSD	Internet
chronic low back pains	Internet

Listing 5: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
CRPS, severe nonresponsive to other treatment back or neck pain	Internet
abdominal pain due to chrons	Internet
Severe, unremitting, rapid onset neuropathic pain not controlled by long and other short-acting opioids, and which are unresponsive to non-opioid medications, a cause is known, and for which other surgical/ injection treatment options have failed.	Internet
Post-laminectomy Pain Syndrome, Complex Regional Pain Syndrome. For episodes of acute exacerbation from activity.	Internet
cancer pain, spinal cord injury pain. nerve pain, muscularskeletal pain	Internet
CANCER, COMPRESSION FRACTURES	Internet
Intractable back pain in patients with high opioid tolerance	Internet
Chronic back pain Chronic pain secondary to ischemic PVD/non-healing leg wounds	Internet
sickle cell, abdominal pain	Internet
We have a patient with chronic abdominal pain, chronic pain after ovarian cancer and a patient with uncontrollable pain after back surgery. Can they use it without a long acting narcotic? All of my patients are on a long acting narcotic.	Internet
low back, post lami syndrome, resistant RSD, Other chronic pain conditions	Internet
where is guideline available?	Internet
Postlaminectomy syndrome; severe neuropathy; chronic severe trauma patients-paraplegic,etc.	Internet
Chronic abdominal pain related to multiple surgeries, surgical complications or complex GI issues	Internet
Cancer, spine diseases, severe rheumatologic disease	Internet
non functioning GI tract,or to avoid high pill burden, or in cases of possible med diversion, or in cases where patient and care giver cannot follow a schedule of oral meds.	Internet
severe cases of RSD that are not responsive to DRG blocks, and around the clock opiod therapy	Internet
Profound end-stage RA	Internet
post laminectomy syndromes, severe spinal stenosis, severe total body pain syndromes	Internet
I only have one pt with significant back pain and an extensive operative history-otherwise it is only used for cancer pts	Internet
Failed back syndrome, Chronic low back and neck pain, RSD	Internet
patients who have allergies to dilaudid and morphine and patients on opiates for dressing changes/wound care.	Internet

Listing 5: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
SPINAL STENOSIS, ARTHRITIS, FIBRO	Internet
spinal myelopathic pain sickle cell crisis neuropathic pain with acute exacerbation is often refractory to slower onset rescue medicines sickle cell crisis pain can be abrupt and refractory to slower acting agents	Internet
Chronic post surgical (abdominal, lumbar, orthopedic) pain refractory to other narcotics, Advanced chronic pancreatitis pain. dor pain that is refractory to higher doses of conventional narcotics.	Internet
lower back pain, neck pain, rsd, ms rheumatoid arthritis	Internet
Failed back surgery pain, CRPS	Internet
unspecified chronic pain uncontrolled by all other means	Internet
Life limiting illnesses such as COPD, CHF, etc. Those that are progressive, irreversible and terminal. As a palliative care physician I utilize TIRF medicine to manage negative symptoms of conditions that have a chronic pain(as well as dyspnea) component. I do not treat "chronic pain" patients but all conditions I do see have or have the potential to have a pain component.	Internet
failed back syndrome	Internet
chronic pain due to injury, oa, lumbar ddd	Internet
Complex Regional Pain Syndrom	Internet
Failed Surgical Syndrome, Peripheral Neuropathy	Telephone
Prescriber reported use of TIRF product for Severe Musculoskeletal and Neuropathic-type pain conditions. - Question 10	Internet
sever chronic Pain from sever arthritis or back surgery if they are opioid tolerant	Internet
Chronic sacral pain, chronic back pain that surgery has not helped and patient can't get any relief during BM	Internet
Migraines	Internet
Breakthrough pain in cancer patients, Chronic neuropathic pain and failed back surgery syndrome due to nerve damage/irritation in patients that cannot swallow due to other GI/craniofacial medical conditions.	Internet
Post thalamic stroke pain syndrome	Internet
TRIGEMINAL NEURALGIA	Internet
chronic uncontrolled pain, especially abdominal pain and spine pain conditions	Internet
chronic neuropathic pain	Internet
RSD	Internet

Listing 5: Listing of Potential Adverse Events and/or Product Complaints Reported by Modality

Verbatim Text	Modality of Report
Patients with chronic wounds prior to wound care	Internet
intolerant to oral opioids due to intestinal absorption problems, cancer pain.	Internet
CHRONIC SPINAL RELATED PAIN SYNDROMES	Internet
Burning mouth syndrome, short gut syndrome	Internet
cancer associated pain, chronic arthritis	Internet
spinal related pain, joint pain,	Internet
Prescriber reported use of TIRF product for Refractory Neuropathic severe episodic pain.	Internet
Prescriber reported use of TIRF product for primarily chronic spinal or musculoskeletal pain - may or may not be related to their underlying cancer diagnosis.	Internet
Prescriber reported use of TIRF product for Arthritis, migraines, neuropathic pain.	Internet
Prescriber reported use of TIRF product for back pain.	Internet
Where do I obtain this information?	Internet
I work in inpatient oncology. We have been taught by our pharmacy that the use of certain TIRF medications, specifically actiq, is acceptable for inpatient procedure pain control (such as bone marrow aspiration and biopsy) although this seems to be in conflict with the product labeling which specifically contraindicates use for acute operative pain.	Internet
Chronic regional pain syndrome; advanced degenerative joint disease; medullary sponge kidney.	Internet
Back pain. Neuropathy	Internet
chronic intractable head/facial pain after MVA with facial implants.	Internet
Failed back surgery. Lumbar radiculopathy	Internet
FAILED BACK SYNDROME , NON OPERATIVE CERVICAL OR LUMBAR DISC DISEASE	Internet
scoliosis, neuropathic leg pain	Internet
Spine related, radiculopathy, neuropathy	Internet
Besides cancer pain, I have used TIRF meds for avascular necrosis with joint destruction when regular opioids were required	Internet
spinal stenosis, severe joint OA, chronic pain s/p multi trauma	Internet
Breakthrough pain, easier application, patients with Nausea/Vomiting, or difficulty with PO routes of medication, Arthritis, Refractory or Chronic Neuropathy/Neuralgia responsive to opiates, Degenerative Disc Disease, Chronic wounds or complications, Dental complications or Mucositis, and Metastatic Disease	Internet

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May 4, 2016

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

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Not Applicable
eCTD Sequence Number: 0023

Dear Drug Master File Staff:

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

McKesson hereby provides the Drug Master File Staff 48-Month REMS Supplemental Assessment Report for Transmucosal Immediate-Release Fentanyl (TIRF), version 1, dated April 25, 2016.

Sincerely,

Gina Melazzo, U.S. Agent
Senior Regulatory Project Manager, Regulatory Affairs
Accenture, LLP
610-407-1732
610-407-8483 (Fax)
gina.melazzo@accenture.com

Attachments: Table of Contents for the submission
Electronic Submission Specifications

Supplemental Report to the 48-Month Assessment

Module Section	Description
1.2 Cover Letter	Cover Letter
1.16 – Risk Management Plans	REMS History Supplemental Report to the 48-Month Assessment TIRF REMS Supplemental Assessment Protocol and Analysis Plan TIRF REMS– Supplemental Assessment Study Report TIRF Persistency Analysis Protocol TIRF Persistency Analysis Final Report Supplemental File 1: TIRF Product NDC Codes Supplemental File 2: NDC Codes for Opioid Analgesics

Electronic Submission Specifications

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

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

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	12.1.5337.5000
Virus Definition Date	05/02/2016 rev. 11
Submission Size	Approx. 4.4 MB

The IT point of contact for this submission is:

Name	Matt Francis
Phone Number	1-610-407-1854
Email Address	Matthew.p.francis@accenture.com

TIRF REMS Access Program Assessment

Supplemental file 1: TIRF product NDC codes

Product	NDC	Manufacturer
ABSTRAL 03/2011 GNB	42747022104 TAB SL 100MCG 4	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022132 TAB SL 100MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022204 TAB SL 200MCG 4	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022232 TAB SL 200MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022304 TAB SL 300MCG 4	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022332 TAB SL 300MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022404 TAB SL 400MCG 4	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022432 TAB SL 400MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022632 TAB SL 600MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022804 TAB SL 800MCG 4	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	42747022832 TAB SL 800MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033132 TAB SL 100MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033232 TAB SL 200MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033332 TAB SL 300MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033404 TAB SL 400MCG 4	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033432 TAB SL 400MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033632 TAB SL 600MCG 32	GALENA BIOPHARMA
ABSTRAL 03/2011 GNB	57881033832 TAB SL 800MCG 32	GALENA BIOPHARMA
ACTIQ 04/1999 TVN	63459050230 LOZ 200MCG 30	TEVA CNS
ACTIQ 04/1999 TVN	63459050430 LOZ 400MCG 30	TEVA CNS
ACTIQ 04/1999 TVN	63459050630 LOZ 600MCG 30	TEVA CNS
ACTIQ 04/1999 TVN	63459050830 LOZ 800MCG 30	TEVA CNS
ACTIQ 04/1999 TVN	63459051230 LOZ 1200MCG 30	TEVA CNS
ACTIQ 04/1999 TVN	63459051630 LOZ 1600MCG 30	TEVA CNS
FENTANYL CIT 04/1998 MKR	00406920230 LOZ 200MCG 30UD	MALLINCKRODT
FENTANYL CIT 04/1998 MKR	00406920430 LOZ 400MCG 30UD	MALLINCKRODT
FENTANYL CIT 04/1998 MKR	00406920630 LOZ 600MCG 30UD	MALLINCKRODT
FENTANYL CIT 04/1998 MKR	00406920830 LOZ 800MCG 30UD	MALLINCKRODT
FENTANYL CIT 04/1998 MKR	00406921230 LOZ 1200MCG 30UD	MALLINCKRODT
FENTANYL CIT 04/1998 MKR	00406921630 LOZ 1600MCG 30UD	MALLINCKRODT
FENTANYL CIT 09/2006 TEV	55253007001 LOZ 200MCG 1	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007030 LOZ 200MCG 10X3 BLISTER (30)	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007101 LOZ 400MCG 1	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007130 LOZ 400MCG 10X3 BLISTER (30)	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007201 LOZ 600MCG 1	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007230 LOZ 600MCG 10X3 BLISTER (30)	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007301 LOZ 800MCG 1	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007330 LOZ 800MCG 10X3 BLISTER (30)	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007401 LOZ 1200MCG 1	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007430 LOZ 1200MCG 10X3 BLISTER (30)	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007501 LOZ 1600MCG 1 0075-01	TEVA PHARMACEUTICA
FENTANYL CIT 09/2006 TEV	55253007530 LOZ 1600MCG 10X3 BLISTER (30)	TEVA PHARMACEUTICA
FENTANYL CIT 10/2011 P.H	49884045955 LOZ 200MCG 30	PAR PHARM
FENTANYL CIT 10/2011 P.H	49884046055 LOZ 400MCG 30	PAR PHARM
FENTANYL CIT 10/2011 P.H	49884046155 LOZ 600MCG 30	PAR PHARM
FENTANYL CIT 10/2011 P.H	49884046255 LOZ 800MCG 30	PAR PHARM
FENTANYL CIT 10/2011 P.H	49884046355 LOZ 1200MCG 30	PAR PHARM
FENTANYL CIT 10/2011 P.H	49884046455 LOZ 1600MCG 30	PAR PHARM
FENTORA 10/2006 TVN	63459054128 TAB BUCCAL 100MCG 28	TEVA CNS
FENTORA 10/2006 TVN	63459054228 TAB BUCCAL 200MCG 28	TEVA CNS
FENTORA 10/2006 TVN	63459054328 TAB BUCCAL 300MCG 28	TEVA CNS
FENTORA 10/2006 TVN	63459054428 TAB BUCCAL 400MCG 28	TEVA CNS
FENTORA 10/2006 TVN	63459054628 TAB BUCCAL 600MCG 28	TEVA CNS
FENTORA 10/2006 TVN	63459054828 TAB BUCCAL 800MCG 28	TEVA CNS
LAZANDA 10/2011 DP7	13913000901 NASAL SPRAY 100MCG 1	DEPOMED INC
LAZANDA 10/2011 DP7	13913001001 NASAL SPRAY 400MCG 1	DEPOMED INC
SUBSYS 03/2012 INY	20482000110 PUMP SPRAY 100MCG 10	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000130 PUMP SPRAY 100MCG 30	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000210 PUMP SPRAY 200MCG 10	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000230 PUMP SPRAY 200MCG 30	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000410 PUMP SPRAY 400MCG 10	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000430 PUMP SPRAY 400MCG 30	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000610 PUMP SPRAY 600MCG 10	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000630 PUMP SPRAY 600MCG 30	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000810 PUMP SPRAY 800MCG 10	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482000830 PUMP SPRAY 800MCG 30	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482001201 PUMP SPRAY 1200MCG 1UD	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482001215 PUMP SPRAY 1200MCG 30	INSYS THERAPEUTICS
SUBSYS 03/2012 INY	20482001615 PUMP SPRAY 1600MCG 30	INSYS THERAPEUTICS

Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program 48-Month Supplemental Assessment Report
Report Date	25 APR 2016
Reporting Timeframe:	29 OCT 2014 to 28 OCT 2015
Document Number:	FINAL v 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.

Confidentiality Statement

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LIST OF TABLES

LIST OF ABBREVIATIONS

FDA	Food and Drug Administration
IR	Immediate Release
KAB	Knowledge, Attitude, and Behavior
LRx	IMS Longitudinal Prescription Database
LTC	Long-term care
NDA	New Drug Application
NPA	National Prescription Audit
REMS	Risk Evaluation and Mitigation Strategy
TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl product(s)
TIRF REMS Access	REMS program for TIRF medicines
TIRF Sponsors	The group of sponsors that are submitting this REMS
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

1 OVERVIEW

The Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of Transmucosal Immediate-Release Fentanyl (TIRF) medicines. The TIRF REMS Access program was approved by the FDA on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS®, SUBSYS® and generic versions of these TIRF medicines. The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval.

This report completes the response to FDA's 36-Month FDA Acknowledgement Letter, initially received on 04 August 2015, requesting additional analyses of the REMS data. The group of Sponsors who are submitting this 48-Month REMS Assessment Report Supplemental Report (Actavis Laboratories FL, Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Insys Therapeutics Inc., Mallinckrodt Pharmaceuticals, Mylan, Inc., Par Pharmaceutical, Inc., and Sentynl Therapeutics, Inc.) are herein referred to as TIRF Sponsors. One company joined the TRIG since the finalization of the 48-Month FDA Assessment Report submitted in December 2015: Sentynl Therapeutics replaced Galena Biopharma, Inc. on 09 January 2016. The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. This report has been prepared by United BioSource Corporation (UBC).

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

Table 1 TIRF Medicines

Product Name (active ingredient)/formulation
NDA 22510, ABSTRAL (fentanyl) sublingual tablets
NDA 20747, ACTIQ (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 21947, FENTORA (fentanyl) buccal tablet
NDA 22569, LAZANDA (fentanyl) nasal spray
NDA 22266, ONSOLIS (fentanyl) buccal soluble film
NDA 202788, SUBSYS (fentanyl) sublingual spray
ANDA 77312, fentanyl citrate oral transmucosal lozenge
ANDA 78907, fentanyl citrate oral transmucosal lozenge

The FDA's communication included multiple new requests to be incorporated into the 48-Month REMS Assessment Report. Due to the timing of the FDA's correspondence, requested items #2 and #3 (Table 2) were not included in the 48-Month REMS Assessment Report. As communicated to the FDA on 08 September 2015, these items are reported in this 48-Month REMS Supplemental Report to be submitted to the FDA on or before 04 May 2016.

In addition to items #2 and #3, the FDA's feedback requested additional analyses for the patient and prescriber Knowledge, Attitude, and Behavior (KAB) surveys. The prescriber survey was to include an analysis of demographics of the prescriber survey respondents compared to the

demographics of the general population of TIRF prescribers. The patient survey was to include an analysis of demographics of the patient survey respondents compared to the demographics of patients receiving a TIRF product.

Analyses in this Supplemental Report cover the same time period as the 48-Month FDA Assessment Report submitted in December 2015.

Table 2 36-Month FDA Assessment Report: FDA Acknowledgement Letter Requests

Request Number*	FDA Request
2.	**IMS Study** To assess the TIRF REMS goal of prescribing and dispensing TIRF products only to appropriate patients, which includes use only in opioid-tolerant patients, conduct the following analysis: 1. Identify a health care database that includes an adequate number of TIRF product users. Within that database, by year, provide the number of total unique patients dispensed an initial prescription for a TIRF product in the outpatient setting. 2. Determine what proportion of those total unique patients received a prescription for an opioid analgesic product prior to the prescription for the TIRF product. 3. Provide these data separately for patients receiving an opioid analgesic within the 7-days prior and within the 30-days prior to the initial TIRF prescription. Before embarking on this analysis, provide to FDA your choice of database and the estimated number of TIRF users in the database so that we can determine if the number is adequate.
3.	**Persistency Analysis** We are not able to establish whether the TIRF REMS is achieving the goal of preventing inappropriate conversion between TIRF medicines. To better understand how many people are at risk for inappropriate conversion between TIRF medicines, we need a better idea of how long patients stay on one TIRF and whether they shift between TIRF products or just stop them completely. • Conduct a persistency analysis based on the data available on the prescriptions processed through the switch system used by retail pharmacies. o This analysis should demonstrate the number of patients starting on a TIRF and follow them over weeks and months to summarize their treatment course and change in therapy. o The TIRF products can be grouped together, and the specific drug does not need to be disclosed. • Following the discontinuation of the TIRF, the persistency analysis should also depict what treatment option the patient uses next. This will be either full discontinuation or switching to another TIRF product. • There may be gaps in between prescriptions; 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.

Request Number*	FDA Request
12.	**KAB Data Comparison** Additional comments and recommended revisions to the stakeholder surveys that should be implemented in subsequent surveys follow below: a. Patient survey: (i.) In subsequent Assessment Reports, provide an analysis of how the demographics of the patient survey respondents compare to the demographics of actual TIRF patients. c. Prescriber survey: (i.) In subsequent Assessment Reports, provide an analysis of how the demographics of the prescriber survey respondents compare to the demographics of actual TIRF prescribers.

*Numbering is aligned with the numbering of the FDA requests communicated in the 36-Month FDA's Assessment Report Acknowledgement Letter. Responses for the remaining requests in number 4-12 were included in the 48-Month FDA Assessment Report submitted in December 2015. Item 1 included general FDA feedback on the overall assessment report and required no response.

2 RESULTS

2.1 IMS Study of TIRF Use in Appropriate Patients

In response to the request from the FDA, a statistical analysis was performed to assess the TIRF REMS Access program goal of prescribing and dispensing TIRF products only to appropriate patients, which includes use only in opioid-tolerant patients. This study used data from the IMS Longitudinal Prescription database (LRx), which contains electronic dispensed records of anonymized prescription claims collected from United States (US) retail, long-term care (LTC), and specialty and mail order pharmacies (outpatient only; prescription medications delivered during inpatient stays are not available). The results of that analysis are summarized below.

Patients who filled a TIRF product prescription were identified between 12 March 2012 and 28 October 2015 (the index period). To ascertain previous opioid prescriptions, data were collected from 11 February 2012 to 28 October 2015 (the study period).

The IMS Study Protocol is presented in Appendix 4.1. The complete IMS Study Report, including detailed methodology (Section 5), is presented in Appendix 4.2.

2.1.1 FDA Correspondence

The FDA requested that TRIG provide the choice of database and the estimated number of TIRF users in the database so that the FDA could determine if the number was adequate prior to embarking on the analysis. The TRIG provided estimated raw counts of TIRF users to FDA on 08 September 2015. On 13 November 2015, FDA confirmed that use of IMS data was acceptable, provided that IMS could adequately respond to the noted inconsistency in the number of TIRF users.

(b) (4)

(b) (4)

2.1.2 Objectives

The specific objectives outlined by the FDA were:

- To document by year the number of total unique patients dispensed an initial prescription for a TIRF product in the outpatient setting.
- To determine what proportion of those total unique patients received a prescription for an opioid analgesic product prior to the prescription for the TIRF product.
- To provide data separately for patients receiving an opioid analgesic within the 7 days prior and within the 30 days prior to the initial TIRF prescription.

2.1.3 Eligibility Criteria

(b) (4)

2.1.4 Results

(b) (4)

2.2 Persistency Analysis

2.2.1 Objectives

The specific objectives outlined by the FDA were:

- To demonstrate the number of patients starting on a TIRF medicine and follow them over weeks and months to summarize their treatment course and change in therapy.
- To depict what treatment option the patient used next following the discontinuation of one TIRF product, as applicable. Note: This analysis used only pharmacy switch data related to the TIRF REMS Access program; therefore, no other data concerning non TIRF REMS products were included in the analysis.
- To propose what duration of gap will be considered to mean that the patient has remained on treatment with a TIRF medicine and provide a rationale for selection of that gap length.

2.2.2 Eligibility Criteria

(b) (4)

2.2.3 Results

(b) (4)

(b) (4)

2.3 Knowledge, Attitude, and Behavior Surveys Data Comparison

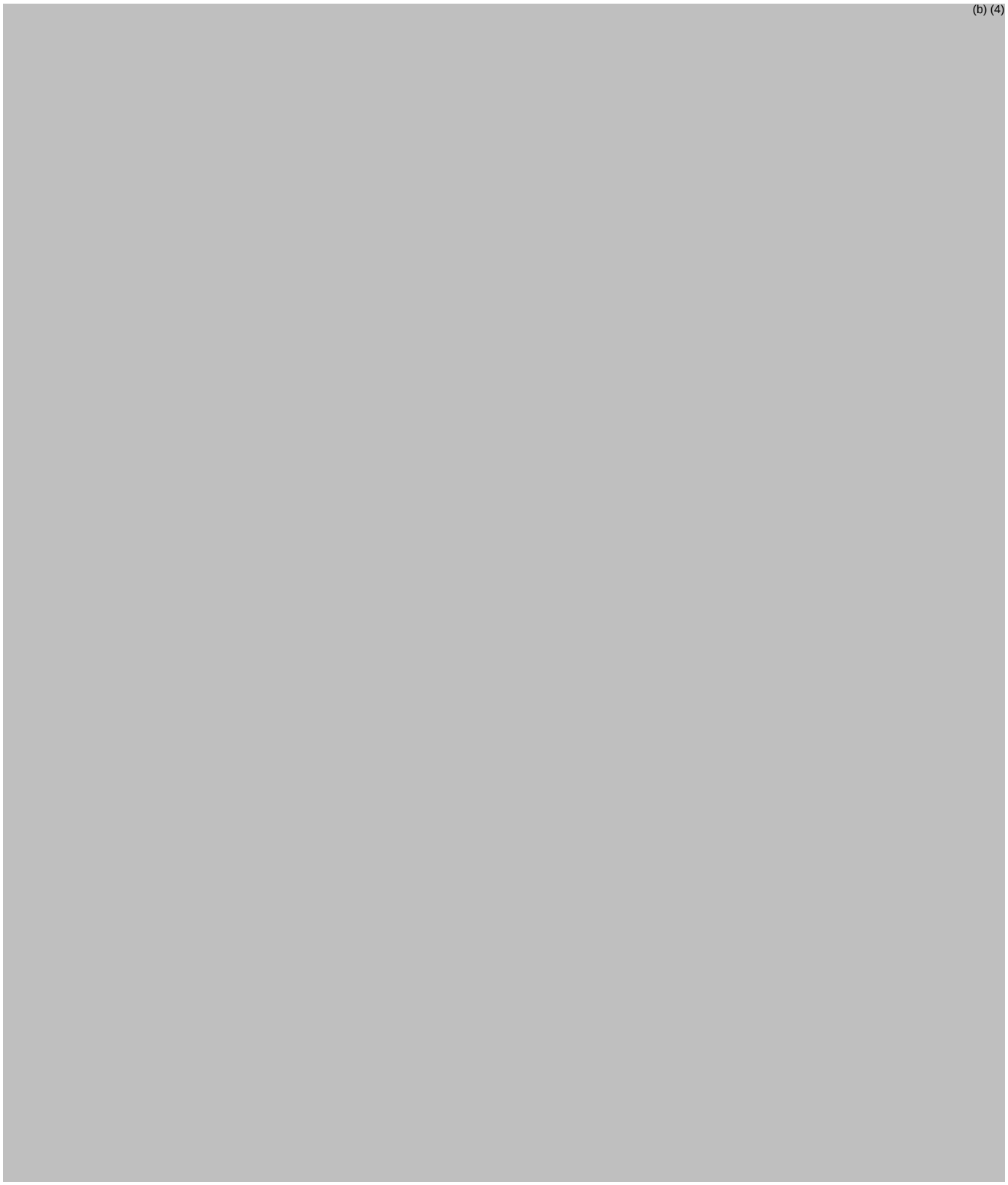
Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements are evaluated through KAB surveys. These surveys are administered to selected prescribers, pharmacies, and patients. FDA requested additional analyses to compare the demographics of prescribers and patients who completed the survey to the general population of prescribers and patients, respectively. Data obtained from IMS Health were used to fulfill this request. It was assumed that these IMS data cover the majority of healthcare providers prescribing and patients receiving TIRF medicines in the outpatient setting.

Results of these additional analyses for the prescriber and patient survey data are discussed in Sections 2.3.1 and 2.3.2.

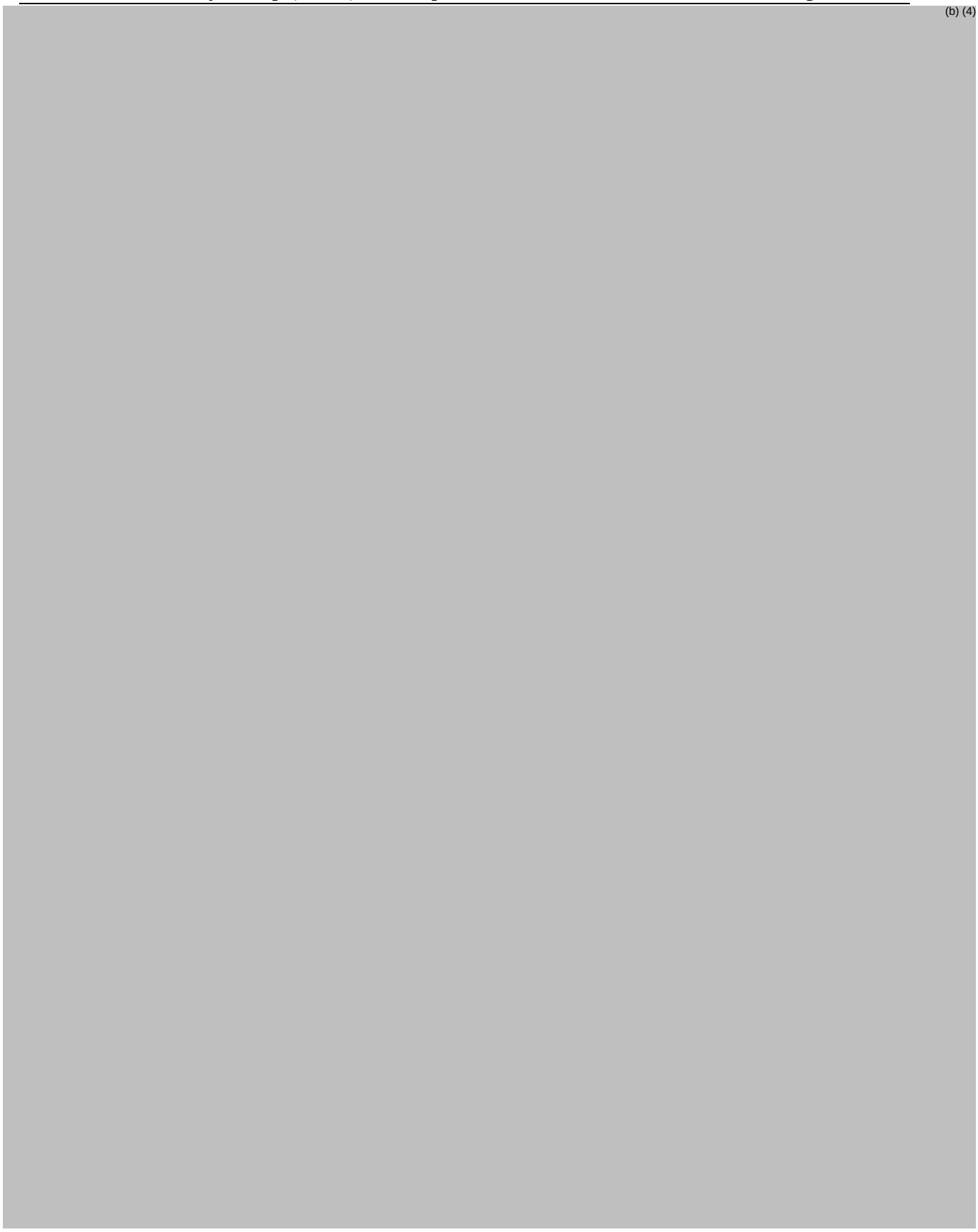
2.3.1 Prescriber Report

(b) (4)

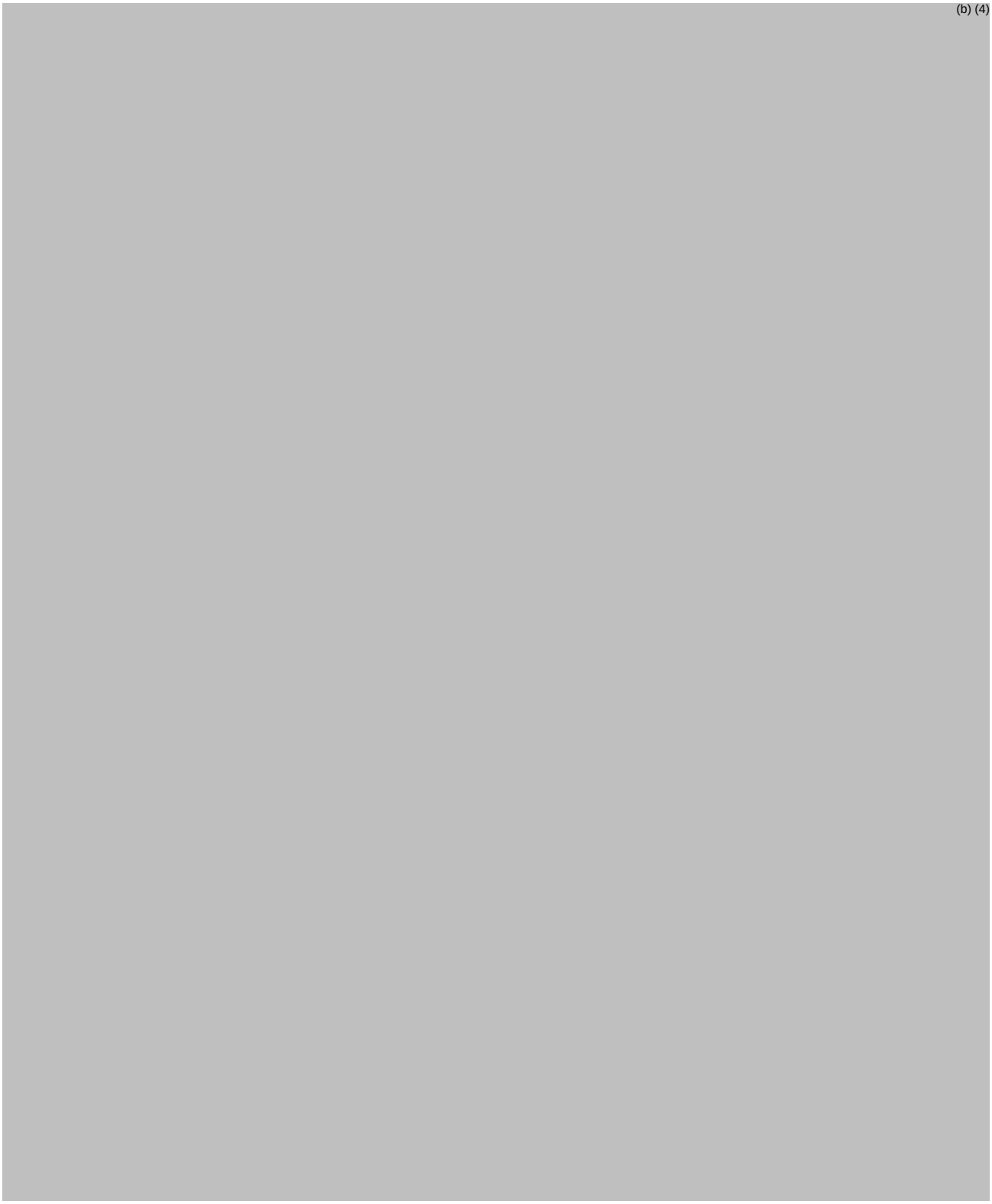
(b) (4)



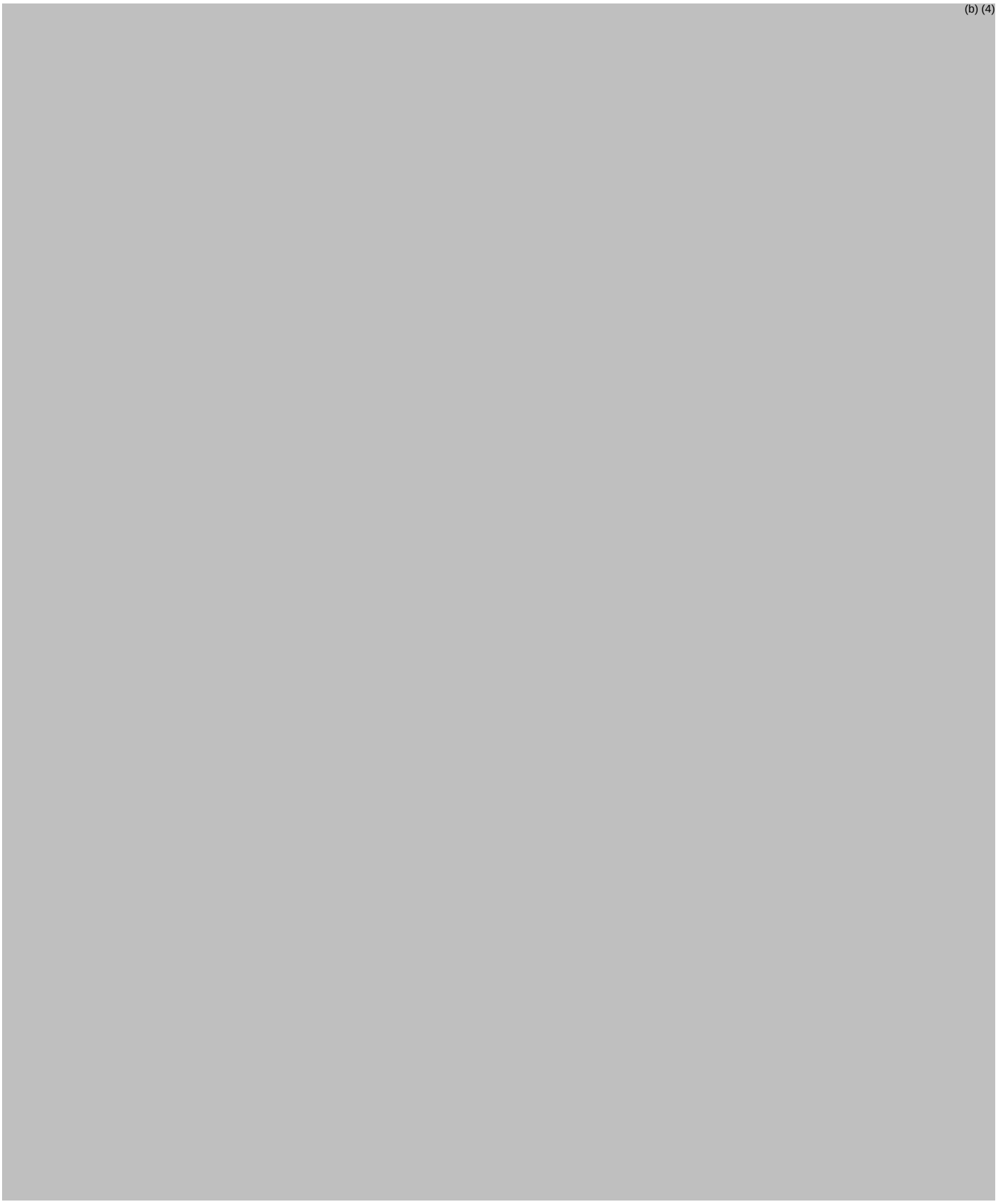
(b) (4)



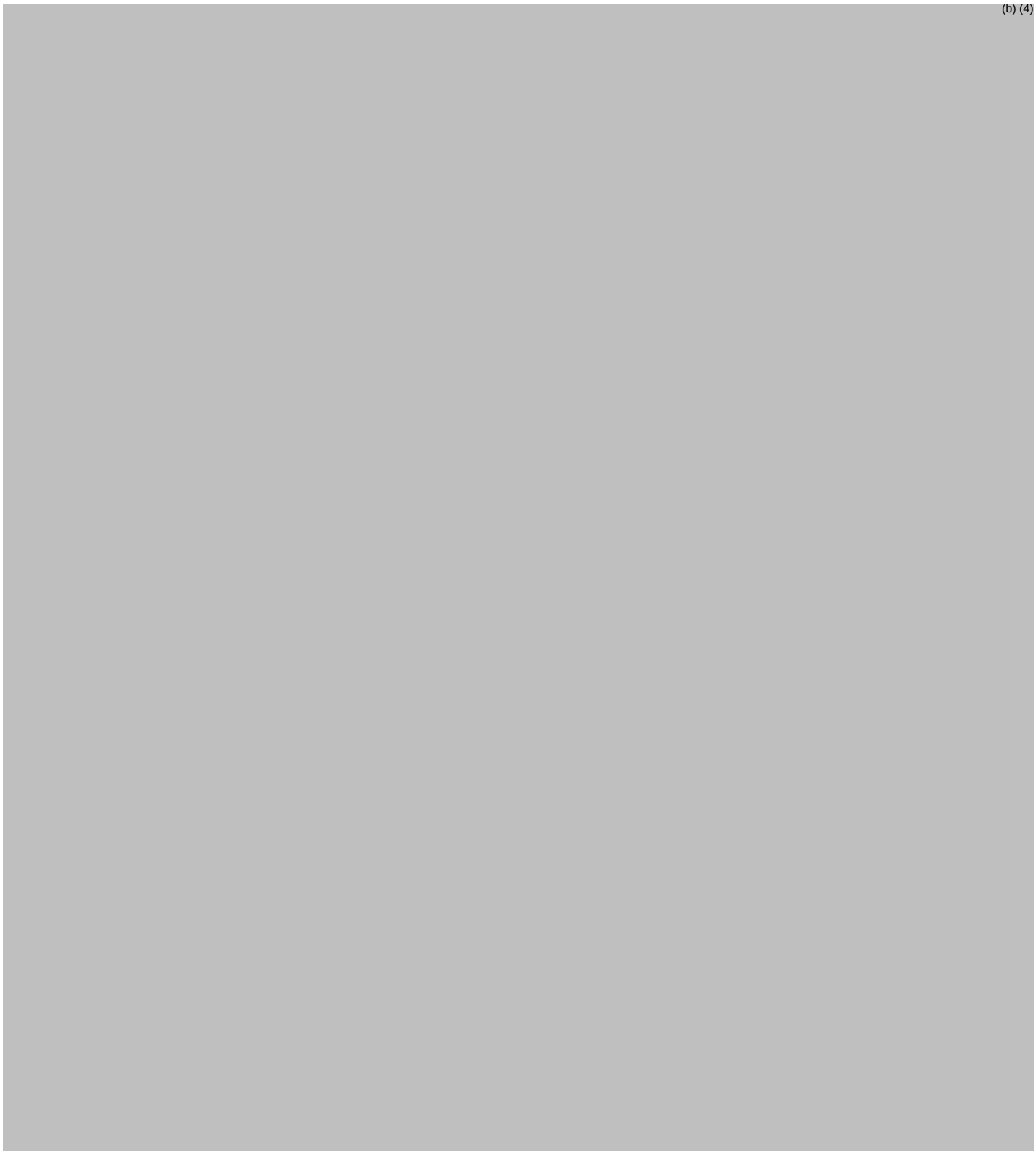
(b) (4)



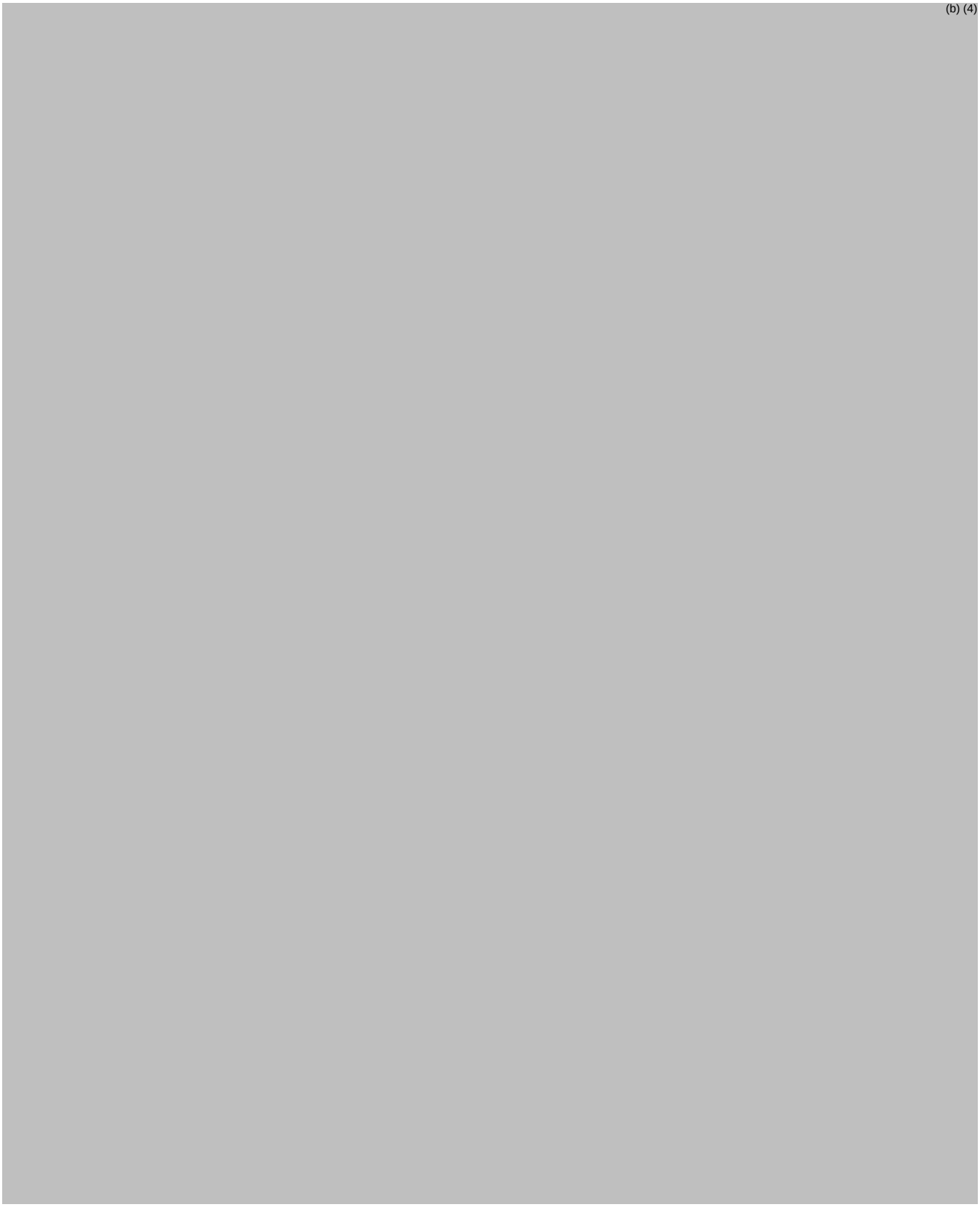
(b) (4)



(b) (4)



(b) (4)



3 DISCUSSION

As part of the evaluation of the TIRF REMS Access program, the FDA requested further statistical analyses to assess if the appropriate patients were being prescribed and dispensed TIRF medicines and to assess patients' persistence on TIRF medicines. In addition, analyses were performed to compare the demographics of prescribers and patients who completed the 2015 KAB surveys to the general population of prescribers and patients, respectively.

The TRIG worked with IMS to conduct a study to determine whether patients receiving a TIRF prescription met the opioid tolerance criteria as dictated by the TIRF REMS Access program. (b) (4)

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A persistency analysis was conducted to assess patients' persistence on TIRF medicines. (b) (4)

For the prescriber KAB analysis of demographics, (b) (4)

(b) (4)

CONCLUSION

This TIRF REMS Access program Supplemental Report (IMS Study, Persistency Analysis, and additional KAB analysis) further characterized TIRF medicine prescription data, patients' persistence while on TIRF medicines, and stakeholder demographic data in response to the FDA's request.

(b) (4)

(b) (4)

The TRIG concludes that the results presented in this TIRF REMS Access program Supplemental Report accurately represent what is occurring overall in the TIRF REMS Access program and what has been previously reported in the annual assessment reports.

4 APPENDICES

4.1 IMS Study Protocol

4.2 IMS Study Report

4.3 Persistency Analysis Protocol

4.4 Persistency Analysis Report

Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Persistency Analysis Protocol
Document Number:	Final Version 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.

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TIRF REMS Access Program Assessment

STUDY REPORT

April 22, 2016

PREPARED FOR
TIRF REMS TRIG
c/o Rachel Bonfanti
United BioSource Corporation

PREPARED BY
IMS Health
Epidemiology and Drug Safety
Real World Evidence Solutions

The information in this document is confidential and proprietary and may not be disclosed to another party unless disclosure is required by law or regulation.

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TIRF R MS ASSESS ENT PR OTO COL AND ANALYSIS PLAN

2-25-2016

PREPARED FOR
TIRF RE MS TRIG
c/o Rachel Bonfanti
United Bi source Cor oration

PRE ARED BY
IMS H ealth
Real orld Evidence Solutions
Epide iology and rug Safety

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Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Persistency Analysis Final Report
Document Number:	Final Version 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsors:	**TIRF REMS Industry Group (TRIG):**
	Actavis Laboratories FL, Inc.
	BioDelivery Sciences International, Inc.
	Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)
	Depomed, Inc.
	Insys Therapeutics Inc.
	Mallinckrodt Pharmaceuticals
	Mylan, Inc.
	Par Pharmaceutical, Inc.
	Sentynl Therapeutics, Inc.

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

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

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

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

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

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

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

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00022: Administrative Change; Change in US Agent**
N/A	N/A	48-Month REMS Supplemental Assessment Report	**Sequence 00023: 48-Month REMS Supplemental Assessment Report**