



SEALED

IN THE DISTRICT COURT OF CLEVELAND COUNTY
STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel.,
MIKE HUNTER,
ATTORNEY GENERAL OF OKLAHOMA

Plaintiff,

vs.

- (1) PURDUE PHARMA L.P.;
- (2) PURDUE PHARMA, INC.;
- (3) THE PURDUE FREDERICK COMPANY,
- (4) TEVA PHARMACEUTICALS USA, INC.;
- (5) CEPHALON, INC.;
- (6) JOHNSON & JOHNSON;
- (7) JANSSEN PHARMACEUTICALS, INC,
- (8) ORTHO-MCNEIL-JANSSEN
PHARMACEUTICALS, INC., n/k/a
JANSSEN PHARMACEUTICALS;
- (9) JANSSEN PHARMACEUTICA, INC.,
n/k/a JANSSEN PHARMACEUTICALS, INC.;
- (10) ALLERGAN, PLC, f/k/a ACTAVIS PLC,
f/k/a ACTAVIS, INC., f/k/a WATSON
PHARMACEUTICALS, INC.;
- (11) WATSON LABORATORIES, INC.;
- (12) ACTAVIS LLC; and
- (13) ACTAVIS PHARMA, INC.,
f/k/a WATSON PHARMA, INC.,

Defendants.

STATE OF OKLAHOMA, S.S.
CLEVELAND COUNTY
FILED In The
Office of the Court Clerk
of Judge Balkman's
consideration

MAY 02 2019

In the office of the
Court Clerk MARILYN WILLIAMS

Case No. CJ-2017-816
Honorable Thad Balkman

William C. Hetherington
Special Discovery Master

SEALED

DEFENDANTS TEVA PHARMACEUTICALS USA, INC.,
CEPHALON, INC., WATSON LABORATORIES, INC., ACTAVIS LLC,
AND ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.'S
MOTION FOR SUMMARY JUDGMENT AND BRIEF IN SUPPORT

EXHIBIT 20 FILED UNDER SEAL

EXHIBIT 20

Initial REMS approval: 12/2011

Most recent modification: 08/2017

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

I. GOALS

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

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

II. REMS ELEMENTS

A. Medication Guide

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

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

B. Elements to Assure Safe Use

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

- a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.
- b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:
 - i. Review the TIRF REMS Access education materials (TIRF REMS Access Education Program), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (Knowledge Assessment).
 - ii. Complete and sign the Prescriber Enrollment Form. In signing the Prescriber Enrollment Form, each prescriber is required to acknowledge the following:
 - a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
 - b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

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

- c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.
- d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
- e) I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.
- f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/remis/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
- g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
- h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.
- i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years**.
- j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
- k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.
- l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS

Access program requirements for prescribers.

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

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

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

been prescribed can result in a fatal overdose.

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

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

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

- 11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
- 12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.
- c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.
- d. TIRF Sponsors will:
- i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.
 - ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:
 - TIRF REMS Access Prescriber Program Overview
 - TIRF REMS Access Education Program
 - Knowledge Assessment
 - Prescriber Enrollment Form
 - Patient-Prescriber Agreement Form
 - TIRF REMS Access Patient and Caregiver Overview
 - Frequently Asked Questions (FAQs)
 - TIRF REMS Access Website
 - iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.
 - iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.
 - v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.
 - vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, Dear Healthcare Provider Letters will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care

physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

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

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

- a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.
- b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).
- c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**

- i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e., chain stores) in the TIRF REMS Access program.
- ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.
- iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

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

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

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

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

- ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.
- iii. Complete and sign the Independent Outpatient Pharmacy Enrollment Form or the Chain Outpatient Pharmacy Enrollment Form for groups of associated pharmacies. In signing the Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form, the authorized pharmacist is required to acknowledge the following:
 - a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
 - b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.
 - c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/remis/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
 - d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
 - e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
 - f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
 - g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
 - h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
 - i) I understand that ALL TIRF medicine prescriptions, regardless of the method

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

- j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
- k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
- l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
- m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
- n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.
- o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

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

e. Closed System Outpatient Pharmacies:

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

- i. Review the TIRF REMS Access Education Program (TIRF REMS Access Education Program) and successfully complete the Knowledge Assessment.
- ii. Complete and sign the Closed System Outpatient Pharmacy Enrollment Form. In signing the Closed System Outpatient Pharmacy Enrollment Form, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:
 - a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
 - b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.

- c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUl/remis/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
- d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
- e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
- f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
- g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
- h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.
- i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines
- j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
- k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.
- l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
- m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. Inpatient Pharmacies:

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

- i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment*.
- ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:
 - a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
 - b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.
 - c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/remis/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
 - d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
 - e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
 - f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.
 - g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
 - h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

- i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
 - j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.
 - k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
 - l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
 - m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.
- g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.
- h. TIRF Sponsors will:
- i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.
 - ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:
 - The TIRF REMS Access Program Overview (Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy or Inpatient Pharmacy, as applicable)
 - TIRF REMS Access Education Program
 - Knowledge Assessment
 - Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)
 - Frequently Asked Questions (FAQs)
 - TIRF REMS Access Website
 - iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.
 - iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.
 - v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

- vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.
- vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.
- viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

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

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

- a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.
- b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.
- c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.
 - i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.
 - ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.
- d. For **closed system outpatient pharmacies**: prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.
 - i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

- ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.
- e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:
 - i. The patient has not filled a prescription for more than six (6) months.
 - ii. The PPAF has expired.
 - iii. The patient is deceased.
 - iv. The patient chooses to no longer participate in the TIRF REMS Access program.
- f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.
- g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.
- h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

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

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

- c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.
 - d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.
 - e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.
 - f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.
 - g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:
 - Dear Distributor Letter
 - Distributor Enrollment Form
 - Frequently Asked Questions
3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e., active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.
 4. For **chain and independent outpatient pharmacies**, TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.
 5. For **closed system outpatient pharmacies**, TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.
 6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a Patient-Prescriber Agreement Form with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed Patient-Prescriber Agreement Form is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access

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

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

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

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