# FDA Opening Remarks

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

August 3, 2018

Sharon Hertz, MD
Director
DAAAP/ODE-II/OND/CDER/FDA

# Approval History of Transmucosal Immediate-Release Fentanyl (TIRF) Medicines

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee
August 3, 2018

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# Overview of Presentation

- Breakthrough Pain in Patients with Cancer
- Regulatory History of Approved TIRF Products
- Regulatory History of TIRF REMS

REMS=Risk Evaluation and Mitigation Strategies

# Breakthrough Pain in Cancer Patients

- **Definition**
  - A transitory exacerbation of pain that occurs on a background of otherwise stable, persistent pain[1]
- **Characteristics**
  - Quick onset
  - Often severe intensity
  - Relatively short duration
- **Interventions**
  - Various pharmacologic and non-pharmacologic interventions
  - TIRF medicines are one pharmacologic option

[1] Portenoy RK, Hagen NA: Breakthrough pain: Definition, prevalence, and characteristics. Pain 41: 273-281, 1990.

# TIRF Medicines

- Currently, 6 NDA products and 4 ANDA products are approved.
- All contain fentanyl, a potent opioid agonist.
- All **indicated** for the management of breakthrough pain in adults with cancer who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.
- All **contraindicated** in the management of pain in opioid non-tolerant patients.

NDA=new drug applications; ANDA=abbreviated new drug applications (generics)

# Characteristics of TIRF Medicines

- Formulated to provide rapid absorption for quick onset of action with short duration of effect.
- The only drugs specifically approved for the treatment of breakthrough pain in adult patients with cancer.

# Major Safety Concerns with TIRFs

- All opioids have serious risks of respiratory depression, which could result in death, possible overdose, misuse, and abuse.

- Specific TIRF safety considerations:
  - Products contain high amount of fentanyl
  - Accidental ingestion of TIRFs by children
  - Improper patient selection (prescription to and usage by opioid non-tolerant patients)
  - Diversion and abuse

# FDA's Challenges Regarding TIRF Applications

- Optimal strategy to balance the patient's need for cancer breakthrough pain management versus the potential public health risk associated with availability of a potent opioid analgesic.

- The population at greatest risk for adverse effects may not be the population that has the greatest need for these products.

# First Approved TIRF Product: Oralet

- 1993: First oral transmucosal fentanyl citrate, tradename Oralet, was approved.
  - *Indication:* Pre-operative sedation in children in a monitored setting.
  - *Formulation*: Raspberry-flavored lozenge on a stick.
  - *Limitations:* Opioid-naïve children could not tolerate the associated adverse events of nausea and vomiting.
- 2001: Application holder ceased marketing of Oralet.
- 2016: Application holder withdrew the NDA, effective 2017.

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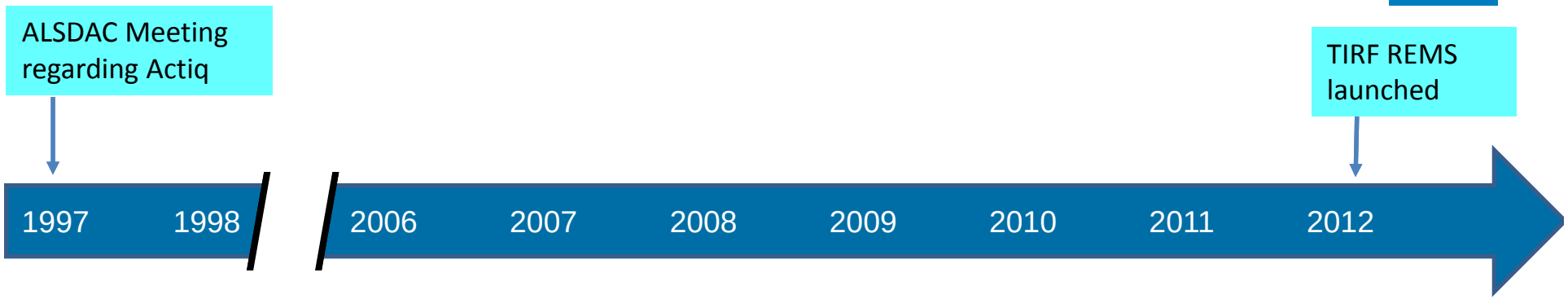


ALSDAC=Anesthetic and Life Support Drugs Advisory Committee

# September 1997 ALSDAC Meeting

- ALSDAC meeting regarding Actiq application.

- Committee voted unanimously that there should be a way found to make Actiq available to those patients who would potentially benefit from it while managing the potential risks to public health.

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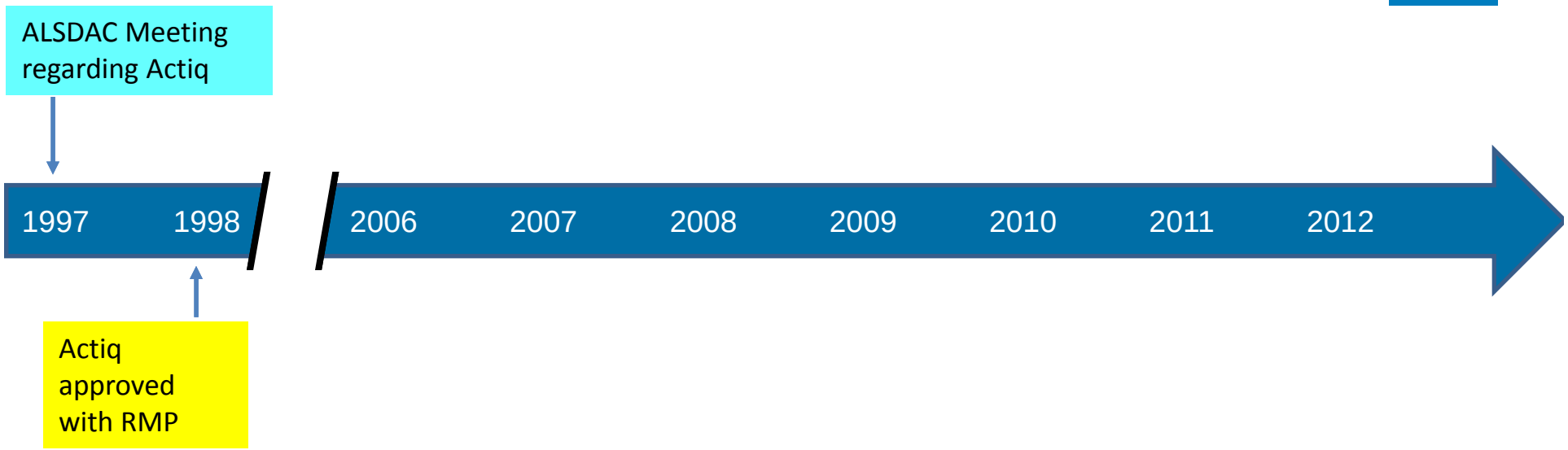


RMP=Risk Management Program

# Primary Components of Actiq's Risk Management Program

- Strong labeling for professionals, patients, and caregivers
- Product-specific design features to increase child safety
- Redundant child-resistant packaging and storage containers
- Professional, patient caregivers, and child educational programs
- Interventions at the point of dispensing

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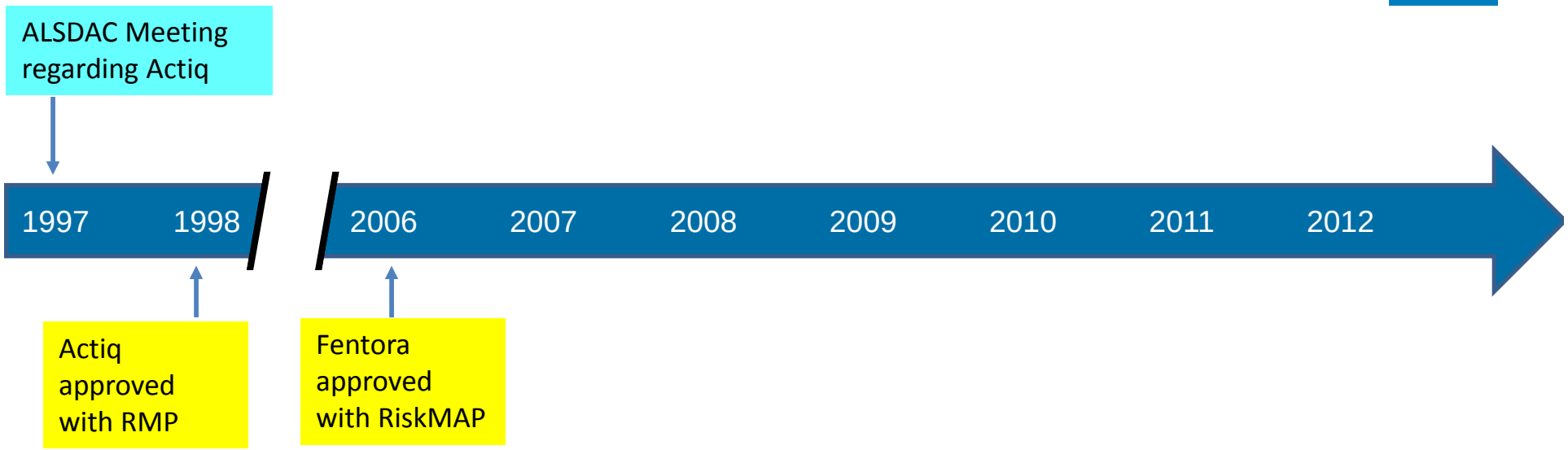


RiskMAP=Risk Minimization Action Plan

# Primary Components of Fentora's RiskMAP

- Implementation of a program and distribution of materials to educate prescribers, pharmacists, nurses, and patients about the risks and benefits of Fentora
- Implementation of a reporting and data collection system for safety surveillance
- Implementation of a plan to monitor, evaluate, and determine the incidence of:
  - Use by opioid non-tolerant individuals
  - Misuse of Fentora
  - Unintended (accidental) exposure to Fentora

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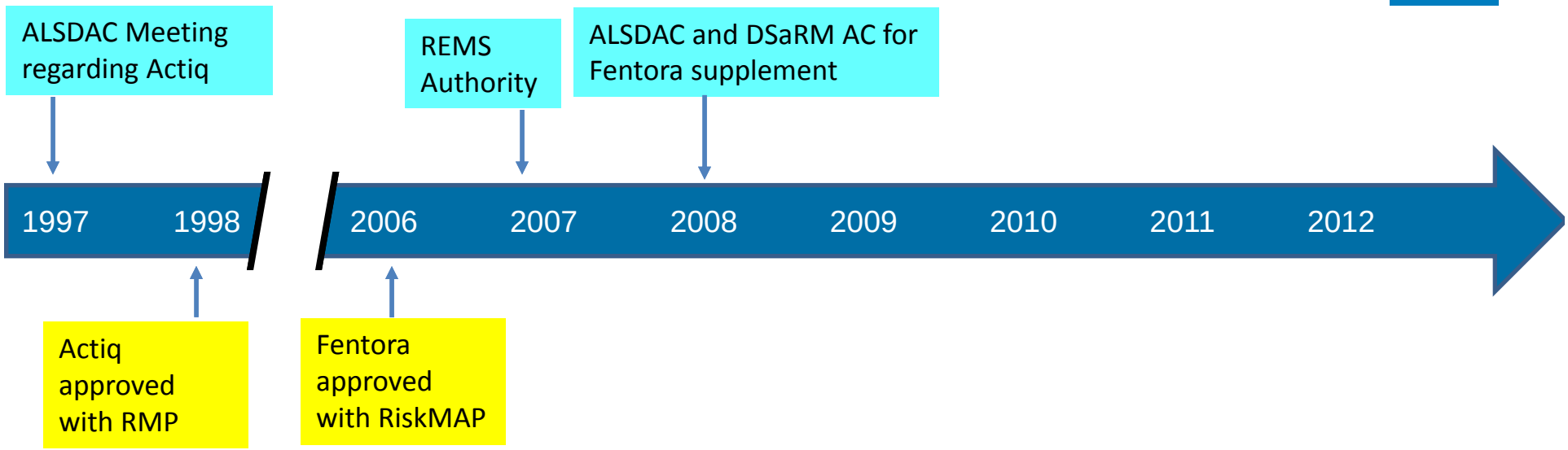


AC=Advisory Committee; DSaRM=Drug Safety and Risk Management; REMS=Risk Evaluation and Mitigation Strategy

# 2008 ALSDAC and DSaRM Advisory Committee Meeting

- ALSDAC and DSaRM Meeting to discuss expanded indication of 2007 Fentora efficacy supplement
- Fentora's RiskMAP Failures
  - Failed to ensure **proper patient selection** for patients with cancer or patients that were opioid-tolerant
  - Failed to provide **adequate education** of prescribers and dispensers
  - Reports of **patient deaths** after being treated with Fentora for migraine headache and chronic low back pain
  - Increasing numbers of **opioid non-tolerant** patients being prescribed Fentora
  - **Improper** dose **titration**, **conversion** from, and **substitution** for Actiq

# 2008 ALSDAC and DSaRM Advisory Committee Meeting

- Committee voted not to expand Fentora's indication (No-17; Yes-3).
- Following the advisory committee meeting, the Agency determined that a REMS was necessary to assure the safe use of oral transmucosal fentanyl products.

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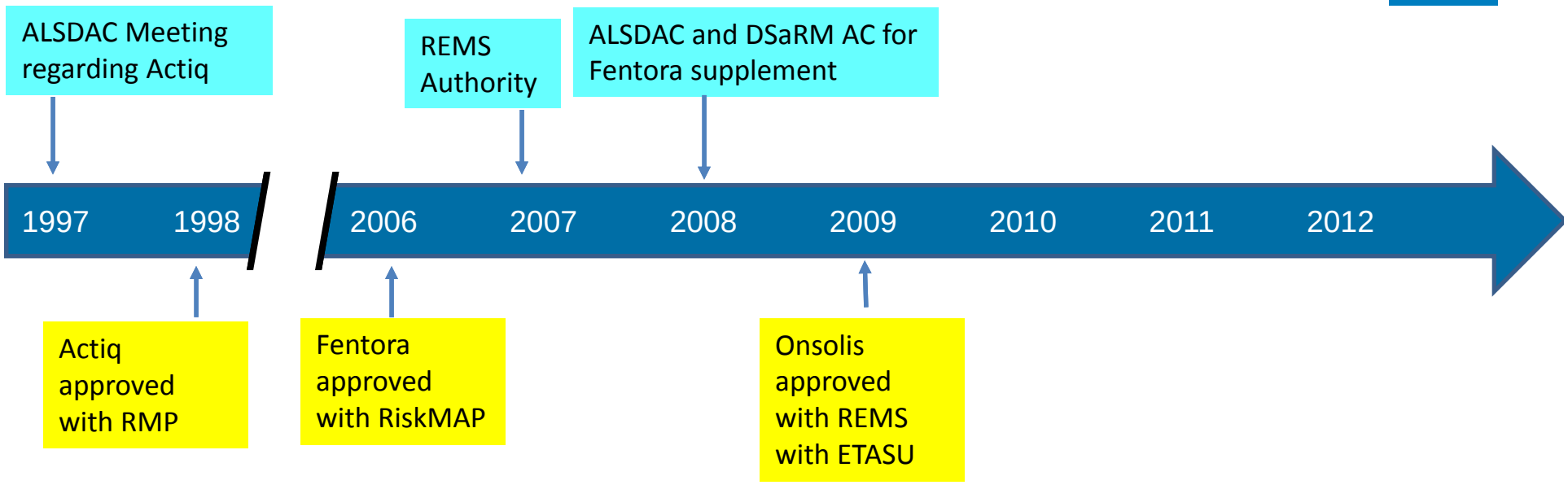


ETASU=Elements to Assure Safe Use

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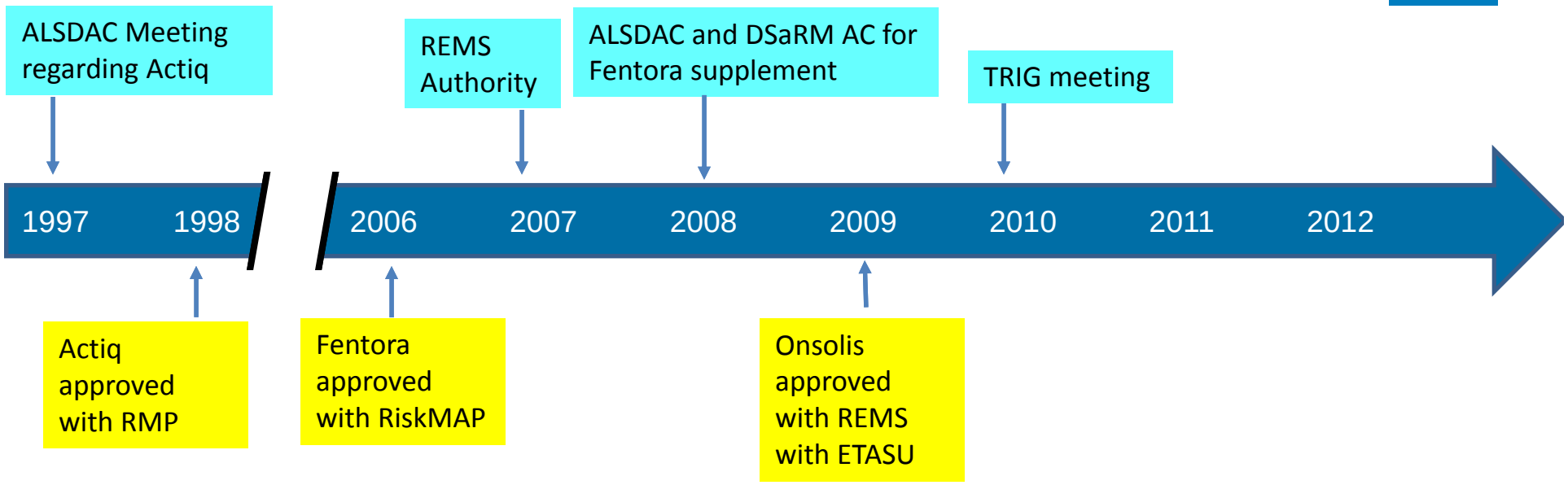
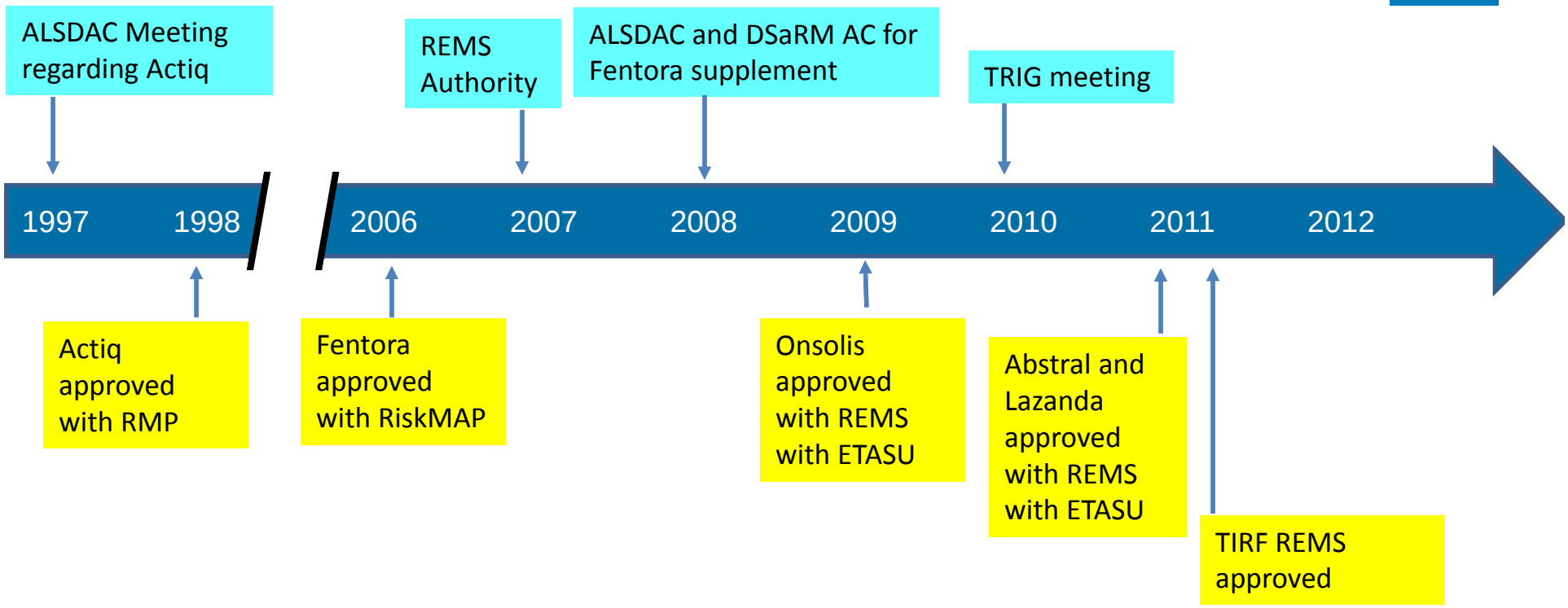



TRIG=TIRF REMS Industry Group

# Select Regulatory History



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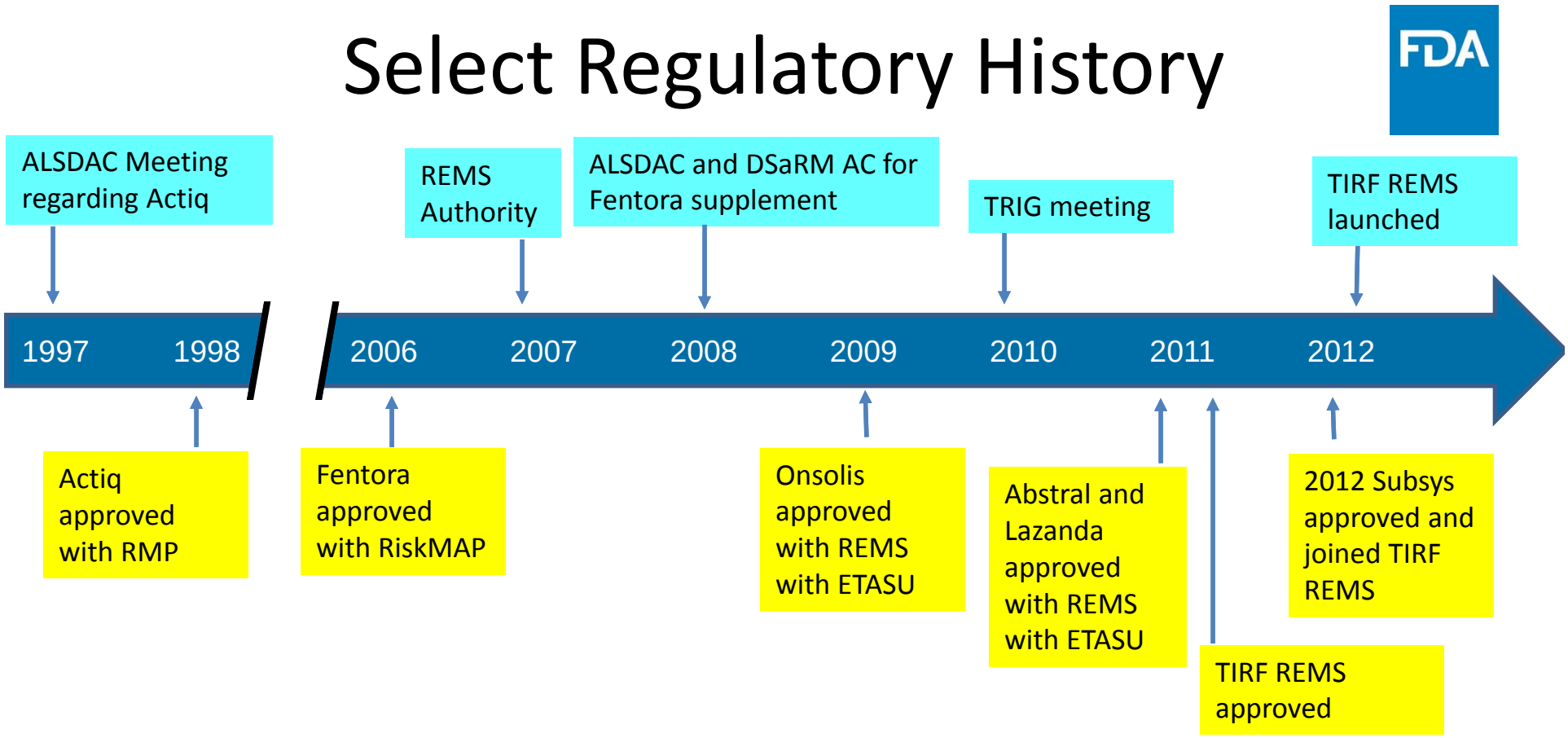

# Approved TIRF Products

| Product Name (application number) [RLD] | Initial Approval | Formulation |
|---|---|---|
| Actiq (NDA 20747) | 11/4/1998 | Solid oral transmucosal lozenge |
| Fentora (NDA 21947) | 9/25/2006 | Buccal tablet |
| Onsolis†(NDA 22266) | 7/16/2009 | Buccal film |
| Abstral (NDA 22510) | 1/7/2011 | Sublingual tablet |
| Lazanda (NDA 22569) | 6/30/2011 | Nasal spray |
| Subsys (NDA 202788) | 1/4/2012 | Sublingual spray |
| Fentanyl buccal (ANDA 079075) [Fentora] | 1/7/2011 | Discontinued |
| Fentanyl citrate (ANDA 207338) [Abstral] | 11/17/2017 | Sublingual tablet |
| Fentanyl citrate (ANDA 078907) [Actiq] | 10/30/2009 | Oral transmucosal lozenge |
| Fentanyl citrate (ANDA 077312) [Actiq] | 10/30/2009 | Discontinued |

Source: Agency generated; Fentanyl citrate troche/lozenge (NDA 20195) tradename, Oralet was approved on 10/4/1993 but was withdrawn (Federal Register notice effective January 30, 2017). It is a TIRF product, but is not included in the TIRF REMS because it was withdrawn; †Onsolis has not been marketed in the US since 2011. RLD=Reference Listed Drug; NDA=New Drug Application; ANDA=Abbreviated New Drug Application (generic).


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# REMS Authority and TIRF REMS

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

August 3, 2018

Cynthia LaCivita, Pharm.D.
Director, Division of Risk Management
OMEPRM/OSE/CDER

# Overview

- REMS Authorities
- TIRF REMS
- TIRF REMS Assessments

# REMS Authorities

# Risk Evaluation and Mitigation Strategy (REMS)

- A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks
- FDA Amendments Act (FDAAA) of 2007 authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks
- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug
- The FDA has authority to require a REMS pre-approval or post-approval

# A REMS may include:

- Medication Guide or patient package insert
- Communication plan
- Elements to Assure Safe Use (ETASU)
- Implementation System

A REMS **must** include:

- Timetable for submission of assessments of the REMS*

**Note: This requirement applies to NDAs and BLAs only.*

# Elements to Assure Safe Use (ETASU)

- Interventions or other actions healthcare providers (HCPs) may need to execute prior to prescribing or dispensing the drug to a patient
- Provides safe access for patients to drugs with known serious risks that would otherwise not be approved or would be withdrawn

# ETASU can include…

- Certification and specialized training of **HCPs** who prescribe the drugs
- Certification of **pharmacies or other dispensers** of the drug
- Dispensing/administration of drug **in limited settings,** e.g., hospitals
- Drug is dispensed/administered only with **evidence of safe-use conditions,** e.g., pregnancy test
- Each patient using the drug is subject to certain **monitoring**
- Enrollment of treated patients in **registries**

The use of an ETASU is not mutually exclusive, they are combined to achieve the goals of the REMS

# Considerations for ETASU

- Should be commensurate with the specific serious risk listed in the labeling of the drug
- Should not be unduly burdensome on patient access to drug, considering in particular, patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care
- Should be similar to other products with ETASU that have similar serious risks
- Should be designed for compatibility with established distribution, procurement, and dispensing systems for drugs

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# Overview of the TIRF REMS

# TIRF REMS

- **Oct 2010 -** The FDA requested that the TIRF Sponsors work together to develop a shared system REMS.

Shared System (SS) REMS

- May encompass multiple drug products and is developed and implemented jointly by at least two or more applicants
- Includes a single REMS document, REMS materials and REMS supporting document across all the products
- Has the potential to minimize the burden to healthcare providers and patients by eliminating the need for them certify or enroll in a separate program for each product.

# TIRF REMS

- Initial approval on December 28, 2011; fully implemented on March 12, 2012
- Also referred to as the TIRF REMS Access Program (TIRF REMS)
- Several modifications have occurred to the REMS since the initial approval.

# Goals and Objectives of the TIRF 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:

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

# TIRF REMS - Key Components

Prescriber Certification (Rx for outpatient use)

Pharmacy Certification

(Outpatient and inpatient dispensing settings)

Patient-Prescriber Agreement Form (PPAF)

(Rx for outpatient use)

# Prescriber Certification

Outpatient Use

- Complete the required education and successfully complete the knowledge assessment
- Enroll initially and re-enroll every 2 years
- Complete the *Patient-Prescriber Agreement Form (PPAF)* for each patient with their first Rx and every 2 years

# Pharmacy Certification

Outpatient Pharmacies

Designated Authorized Representative

- Complete the required education and successfully complete the knowledge assessment
- Enroll initially and every 2 years
- Ensure that all staff are trained
- Prior to dispensing, pharmacy staff must verify the prescriber is certified and the *PPAF* was received within 10 days of the first Rx

# Pharmacy Certification

Inpatient Pharmacies

Designated Authorized Representative

- Complete the required education and successfully complete the knowledge assessment
- Enroll initially and every 2 years
- Ensure that all staff are trained on the REMS
- Establish order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the REMS

# TIRF REMS Education

For prescribers and pharmacists covers the following:

- Increased risk of misuse, abuse, respiratory depression, and overdose, whether accidental or intentional
- Should only be prescribed to patients who are already receiving, and who are tolerant to, around-the-clock opioid therapy
- Indicated for breakthrough pain in cancer patients
- Should not be used in the treatment acute or postoperative pain
- Products are not interchangeable with regard to dosing
- Potential for accidental exposure, particularly in children

# Patient-Prescriber Agreement Form

Required for TIRF medicines prescribed for outpatient use

Patient are passively enrolled with the first prescription.

The *Patient-Prescriber Agreement Form* must be received by the REMS program within 10 days of when the first Rx is filled

# Prescriber Attestations - PPAF

**PPAF attestations, initially approved December 2011**

- My patient is currently using around the clock opioid medication and has been for at least one (1) week.
- My patient is opioid tolerant. Patients considered opioid-tolerant are those who are regularly taking at least:
  - 60 mg oral morphine/day; 25 mcg transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer

# Prescriber Attestations - PPAF

**PPAF Attestations, modified in November 2013**

- I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain

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

# Prescriber Attestations - PPAF

## PPAF Attestations, modified in November 2013

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

# TIRF REMS Assessment

# TIRF REMS Assessment Reports

- The timetable for submission of assessments requires that TIRF Sponsors submit REMS assessment reports at 6 and 12 months from the date of the initial REMS approval, and annually thereafter.
- The Agency has received 7 assessment reports from the members of the TIRF REMS at: 6, 12, 24, 36, 48, 60, and 72 months.
- The TIRF sponsors submit a single assessment report with aggregate data involving all TIRF medicines.

# TIRF Assessment Plan

| Elements | Metric |
|---|---|
| 1 | Enrollment Statistics and TIRF Medicines Utilization Data |
| 2 | Dispensing Data (e.g., authorizations/rejections) |
| 3 | Program Infrastructure |
| 4 | Program Non-compliance and corrective actions |
| 5 | Surveillance Data - addiction, overdose, death, pediatric exposures and opioid non-tolerance |
| 6 | Stakeholder Surveys- knowledge of the risks, safe use and safe storage |

# Today's Agenda

- Industry Presentations/Clarifying questions
- FDA Presentations/Clarifying questions
- Lunch
- Guest Speakers
  - Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI)
  - Centers for Medicare & Medicaid Services (CMS)
- Open Public Hearing
- Charge to the Committees
- Discussion


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# FDA Review of the Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

August 3, 2018

Doris Auth, Pharm.D.

Associate Director

DRISK/OMEPRM/OSE/CDER

# Outline

- Overview of TIRF REMS assessment metrics
- Utilization data
- Data on the operation of the TIRF REMS
- Results of surveys of knowledge
- Impact on patient access and healthcare delivery system burden

# REMS ASSESSMENTS AND TIRF REMS ASSESSMENT METRICS

# General REMS assessment challenges

- Small patient populations and/or low utilization of REMS drugs
- Representativeness of survey respondents
- Outcomes of interest may be difficult to monitor
- Timeliness of studies

**For these reasons, use of multiple metrics and surrogates necessary**

# TIRF REMS goals and objectives

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:

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

**REMS should be designed to minimize burden on healthcare delivery system and not be unduly burdensome on patient access**

# TIRF REMS assessment metrics

## Process indicators

- REMS enrollment and utilization data
- Dispensing data
- Compliance with REMS requirements

## Outcome indicators

- REMS enrollment and utilization data
- Knowledge surveys
- Estimate of use in opioid-tolerant patients
- Estimate of amount of switching between TIRF medicines
- Adverse events
  - Spontaneous reports
  - Surveillance databases

# TIRF REMS ASSESSMENT: UTILIZATION TRENDS

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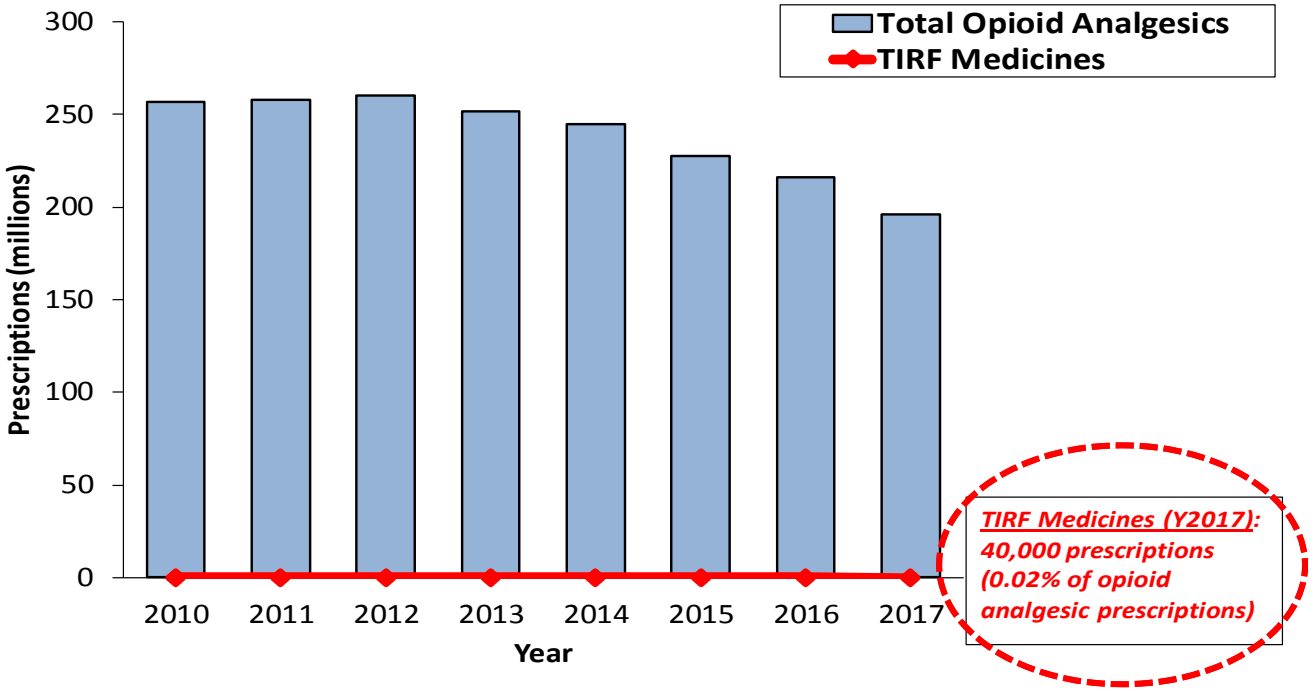
# FDA's Analysis of Outpatient Retail Utilization of Transmucosal Immediate Release Fentanyl (TIRF) Medicines in the U.S.

## 2010-2017

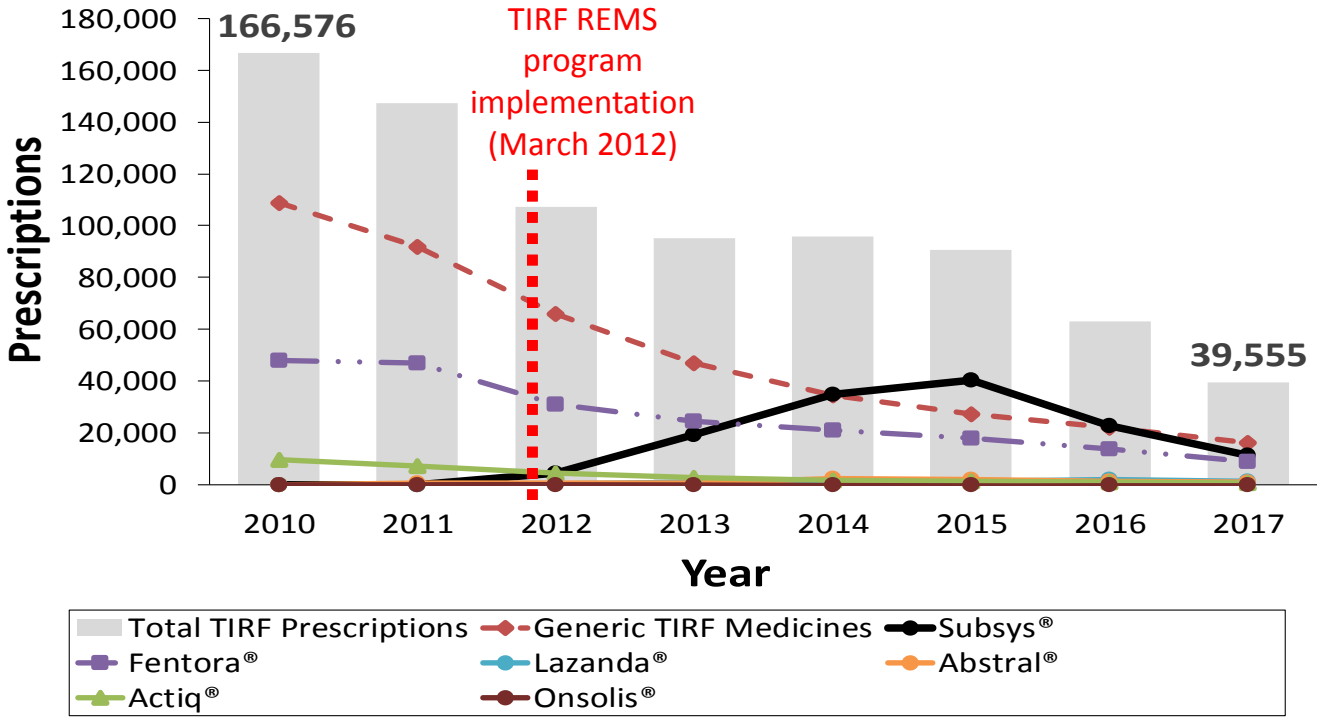
# Prescription Data: Total Opioid Analgesics

National estimates of prescriptions dispensed for opioid analgesic medicines from U.S. outpatient retail pharmacies, 2010-2017




Source: IQVIA National Prescription Audit™ (NPA) and static data 2006-2011 (Extracted March 2017) and data 2012-2017 (Extracted February 2018). Time Period: January 2006- December 2017.

# TIRF Prescription Data*

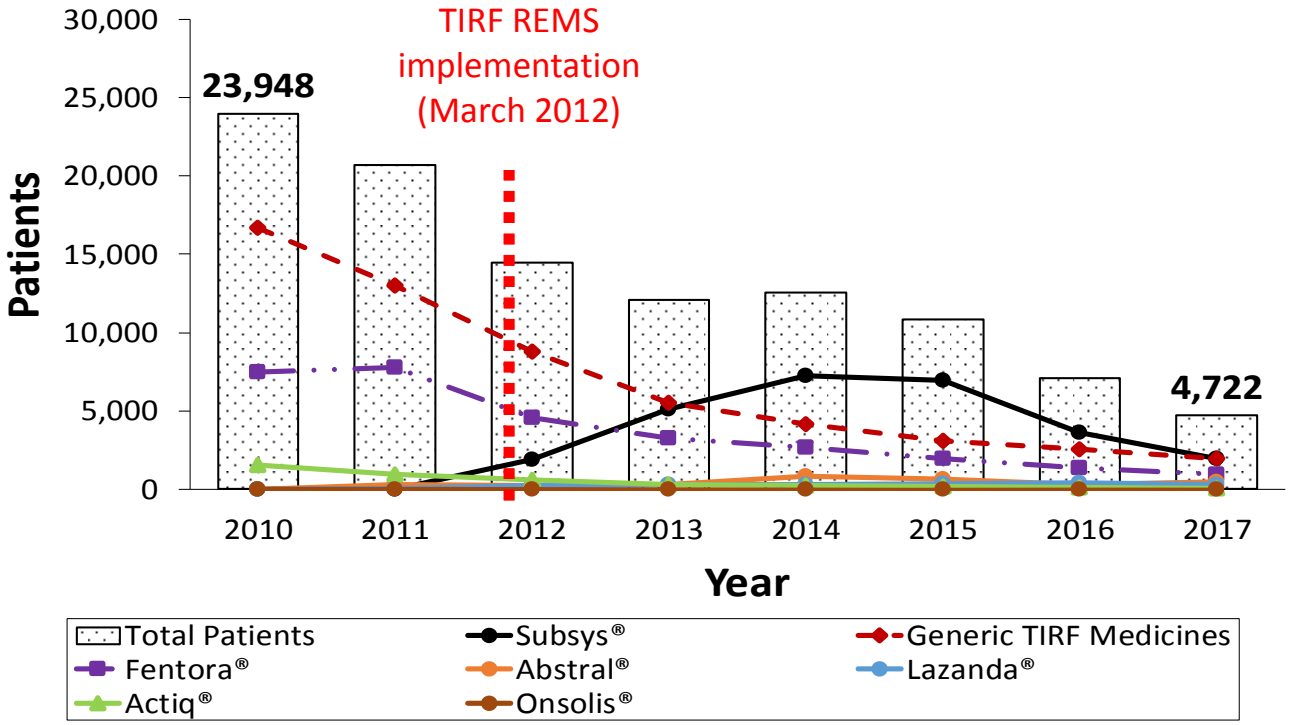



Source: IQVIA National Prescription Audit™. 2010-2017. Data extracted May 2018.

**National estimates of <u>prescriptions</u> dispensed for transmucosal immediate release fentanyl (TIRF) medicines from U.S. outpatient retail pharmacies, 2010-2017**

*Prescription data are not linked to diagnoses; information on patients' opioid-tolerant status or use in patients with cancer and/or break-through pain are not available.

# TIRF Patient Data*




Source: IQVIA Total Patient Tracker™. 2010-2017. Data extracted May 2018.

**National estimates of <u>patients</u> who received prescriptions dispensed for transmucosal immediate release fentanyl (TIRF) medicines from U.S. outpatient retail pharmacies, 2010-2017**

*Data are not linked to diagnoses; information on patients' opioid-tolerant status or use in patients with cancer and/or break-through pain are not available.

# TIRF Prescription Data: Prescriber specialties, 2017

- Anesthesiologists/pain medicine: 34%
- Nurse practitioners/physician assistants: 15%
- Physical Medicine & Rehab: 13%
- Family practice/general practice/internal medicine: 11%
- Oncology: 7%
- Neurology: 4%
- Other specialties or not specified: 16%

Source: IQVIA National Prescription Audit™. 2017. Data extracted March 2018.

# Diagnosis data: Office-based physician surveys, 2017

- Only pain specialists reported use for TIRF medicines
  - Pain, NOS* (G89): 38% of 9,000 drug use mentions for TIRFs
  - Cancer-related conditions (C00-D49): 31%
  - Abdominal and pelvic pain (R10): 31%
- Unknown if TIRF medicines were mentioned for breakthrough pain related to cancer based on the mentioned diagnosis codes.
- Data provide an insight into prescriber intent, but are not directly linked to dispensed prescriptions.
- Information on opioid-tolerant status of the patients are not available.

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™. 2017. Data extracted May 2018.

*not otherwise specified

# Key findings and Gaps-utilization data

| Findings | Gaps |
| --- | --- |
| • TIRF use is low and has been decreasing<br>• Top prescriber specialty: pain specialists | • Declining utilization<br>– Reasons?<br>• Indication for use<br>• Practice settings of non-physician prescribers |

# TIRF REMS ASSESSMENT: REMS OPERATIONS FINDINGS

# TIRF REMS Dispensing

- 92% of TIRF prescriptions are authorized by the REMS
  - 89% experience no REMS related rejections
  - 3% are authorized after one REMS-related rejection
- 8% of TIRF prescriptions are never authorized by the REMS
  - Unclear if patients receive another TIRF prescription, or
  - Another analgesic is prescribed
- Few reports of prescriptions dispensed without a REMS authorization
  - TRIG developing an audit process to identify additional events

# REMS Re-enrollment- Prescribers

- Prescriber enrollments have declined by 30% over the past 3 assessments from
  - 9,096 (48-month) to 8,151 (60-month) to 6,606 (72-month)

- Outreach to a sample of prescribers (3980) and pharmacies (611) to ascertain reasons for not re-enrolling
  - 91% of prescribers & 97% of pharmacies who did not re-enroll did so due to "*Change in Prescribing/Dispensing Data*." For example:
    - Prescriber prescribing in inpatient setting only; or
    - Pharmacy no longer dispensing TIRF medicines for outpatient use only

# REMS Re-enrollment-Pharmacies

- Cumulatively, 41,726 chain stores and 6617 independent stores have enrolled
- Cumulatively, outpatient retail prescriptions dispensed by
  - **65% Independent**
  - 34% Chain
  - 1% Closed-system
- 37,827 chain stores and 3769 independent stores remain enrolled
  - **43% independent Rx re-enrolled**
  - 90% chain Rx re-enrolled
- Is this an access issue?

# Key findings and Gaps - operations data

| Findings | Gaps |
| --- | --- |
| • REMS Processes to authorize TIRF prescriptions functioning well<br>• Decreasing prescriber and pharmacy enrollment | • Reasons for declining enrollment unclear<br>• Impact on patient access |

# TIRF REMS: SURVEY FINDINGS

# REMS Assessment : Survey Design

- Cross-sectional surveys of patients, prescribers, and pharmacists.
- In most cases, the FDA has an opportunity to review survey methodologies and provide any recommended changes to the sponsor prior to survey fielding
  - We encourage all sponsors to complete pre-testing/qualitative testing of the surveys.
  - We ask sponsors to set target knowledge rates; No standard but in most cases it is 80%.
- FDA guidance is currently in development that addresses survey design

# Surveys: Eligibility and Recruitment

| | |
|---|---|
| **Patients/ Caregivers** | • Eligible if 18 or older and had a prescription filled for a TIRF medicine in the past four months<br>• Recruited through the TIRF REMS Access database and a Pharmacy Benefits Manager via direct mail |
| **Prescribers** | • Eligible if enrolled in the TIRF REMS Access Program and prescribed a TIRF medicine in the last six months<br>• Recruited via direct mail from TIRF REMS Access database |
| **Pharmacists** | • Eligible if dispensed TIRF products in the past six months<br>• Recruited from a random sample of pharmacists from the TIRF REMS Access database<br>• Random sample of outpatient pharmacies selected |

# Key findings and Gaps - Surveys

## Findings

- Knowledge consistent across six survey waves
- High level of knowledge of most key risk messages except:
  - Stop TIRF if around-the-clock opioid is stopped.

## Gaps

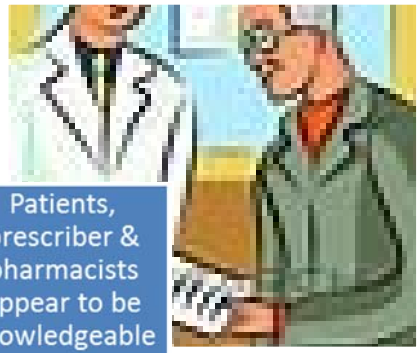
- Low response rates
- Representativeness
- Generalizability of results
- Knowledge ≠ Behavior

# Summary

0.02% of all opioid RX

Approximately 5,000 patients

REMS program processes are functioning as intended.



Patients, prescriber & pharmacists appear to be knowledgeable


Declining utilization and enrollment

# Next presentation

- FDA review of the epidemiologic and surveillance data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# FDA Review of the Epidemiologic and Surveillance Data

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

August 3, 2018

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# TIRF REMS goals and objectives

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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.

# Presentation Agenda

By objective and REMS goal:

1. Sponsors' submission
2. FDA-generated analyses
3. Development of new studies by Sponsors
4. Conclusions from FDA's review

Conclude presentation with overall summary

# TIRF REMS goals and objectives

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.

# Objective 1:
# Ensuring use in appropriate patients

1. **Sponsors' submission**
   - Study of opioid tolerance in patients starting TIRFs
2. **FDA-generated analysis**
   - FDA Adverse Event Reporting System (FAERS)
3. **Sponsors' studies in development**
   - Validation study of opioid tolerance algorithm
   - Study of overdose in patients starting TIRFs
4. **Conclusions from FDA's review**

# Objective 1
# Sponsors' submission

# Sponsors' opioid tolerance study

- Prior opioid tolerance among patients starting TIRFs
- Pharmacy claims-based study in the IQVIA Longitudinal Prescription Database, 2012-2015
- Opioid tolerance determined by claims-based algorithm
  - Calculated average daily dose from prior opioid prescriptions' recorded dosage unit strength, days' supply
  - Criterion: minimum avg. daily dose* for 7 days before TIRF Rx

* Any of the following: 60 mg oral morphine eq, 25 mcg fentanyl/hour, 30 mg oral oxycodone, 8 mg hydromorphone, 25 mg oxymorphone

# How prevalent is opioid tolerance?

- Sponsors' study estimated:
  - 58% of all patients starting a TIRF medicine were opioid-tolerant
  - 45% to 65% in product-specific analyses
- However, one Sponsor's algorithm estimated 77% opioid tolerance, not 58%, using similar data source
- Sponsors then compared the two algorithms' methods
  - Concluded: algorithm that estimated 77% opioid tolerance had no criterion for prior opioid dose
  - Counted 7 days' supply of opioid at any dose
  - Over-estimated opioid tolerance

# Given low prevalence of opioid tolerance, FDA sought more information

- Deaths reported with TIRF medicines
- Adverse events reported in opioid non-tolerant patients
- Accuracy of the claims-based algorithm for opioid tolerance
  - Follows previous research by FDA in claims that also found low prevalence of opioid tolerance prior to use of high-potency opioids

# TIRF spontaneous adverse event reports: deaths, by REMS reporting period

| | Current Reporting Period (72-Month) 29AUG2016-28AUG2017 Number of AEs* | 60-Month Reporting Period 29AUG2015-28AUG2016 Number of AEs* | 48-Month Reporting Period 29AUG2014-28AUG2015 Number of AEs* | 36-Month Reporting Period 29AUG2013-28AUG2014 Number of AEs* |
|---|---|---|---|---|
| **Death** | **549** | 359 | 305 | 414 |

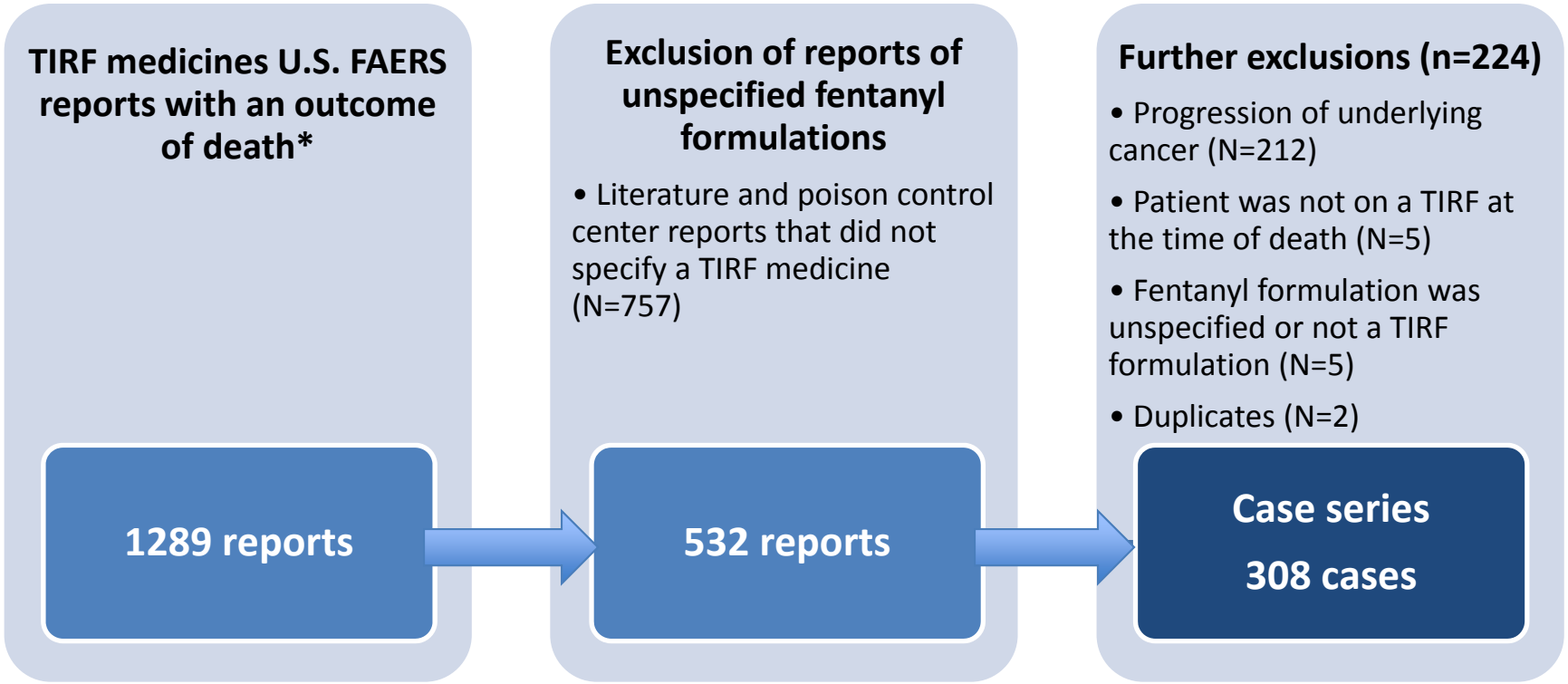
* Literature and poison control cases were excluded

Of the 549 cases, 65% (355/549 reports) lacked sufficient information for an assessment of potential causality.

**Source:** Adapted from 72-Month FDA REMS assessment report, Table 27.
**Sponsor-generated data**

# Objective 1
# FDA-generated analysis
# FDA Adverse Event Reporting System (FAERS)

# FDA review of FAERS death cases




*** U.S. FAERS cases received by the FDA August 29, 2016 - August 28, 2017**

FDA-generated data

# Fatal FAERS cases of TIRF medicines

| Characteristic | N (%) [Total N=308]* |
|---|---|
| **Reason for TIRF medicine use** | |
| Cancer pain | 132 (43%) |
| Non-cancer pain | 14 (5%) |
| Not reported | 162 (52%) |
| **Opioid tolerance per TIRF medicine labeling** | |
| Unable to determine | 59 (19%) |
| Not reported | 249 (81%) |
| **Concomitant opioid [IR or ER] medications** | |
| Yes | 56 (18%) |
| No | 3 (1%) |
| Not reported | 249 (81%) |

*** Select U.S. FAERS cases received by the FDA August 29, 2016 - August 28, 2017**

FDA-generated data

# Fatal FAERS cases of TIRF medicines

| Characteristic | N (%) [Total N=308]* |
|---|---|
| **Cause of death** | |
| Cancer related | 4 (1%) |
| Infection related | 4 (1%) |
| Myocardial infarction | 3 (1%) |
| Accidental overdose† | 1 (<1%) |
| Respiratory depression‡ | 1 (<1%) |
| Suicide§ | 1 (<1%) |
| Other | 3 (1%) |
| Not reported | 291 (94%) |
| **TIRF medicine** | |
| Subsys | 194 (63%) |
| Oral transmucosal fentanyl citrate | 37 (12%) |
| Fentora | 26 (8%) |
| Abstral | 16 (5%) |
| Actiq | 14 (5%) |
| Lazanda | 14 (5%) |
| Transmucosal fentanyl [unspecified] | 7 (2%) |

* Select U.S. FAERS cases received by the FDA August 29, 2016 - August 28, 2017

FDA-generated data

† History of illicit drug abuse

‡ Potential abuse/misuse of the TIRF medicine

§ Method of suicide not specified; unclear if drug-related

# FAERS cases of TIRFs used in opioid non-tolerant patients (N=10*)

| |
|---|
| **Cardiac disorders** |
| Angina pectoris† (1), Palpitations (1) |
| **Gastrointestinal disorders** |
| Dental caries (1) |
| **General disorders and administration site conditions** |
| Drug ineffective (2), Drug tolerance (1), Pain (reported as uncontrolled pain) (1) |
| **Nervous system disorders** |
| Dizziness (1), Headache (1), Somnolence (1) |
| **Psychiatric disorders** |
| Withdrawal syndrome (2), Euphoric mood (reported as euphoria) (1) |

* A case may report more than one adverse event.
† Unlabeled adverse event.
**U.S. cases received by FDA from January 1, 2010 to December 31, 2017**
**FDA-generated data**

# FAERS cases of TIRF medicines: Summary

- Stimulated reporting of deaths due to
  - TIRF REMS Access program contacting patients every 2 years
  - Public awareness of fentanyl overdoses
- Lack of important details in majority of cases
  - Cause of death
  - Concomitant diseases and medications
  - Opioid tolerance status
  - Reasons for TIRF medicine use
- Causal relationship between product and event not required
- No definitive conclusions can be made about these cases

# Objective 1
# Development of new studies by the Sponsors

# Opioid tolerance algorithm validation study

- Sponsors submitted a study protocol to validate claims-based algorithm with medical records
  - 127 patients in Henry Ford Health System, closed healthcare system in Detroit, MI
  - Includes inpatient use and outpatient dispensings
- Protocol undergoing review by FDA, local institutional review board

# Discussion of validation study

| Limitations | Efforts to address limitations |
|---|---|
| Opioid tolerance algorithm may:<br>- Systematically miss sources of opioid<br>- The calculated average daily dose consumed may be inaccurate | Two validation studies:<br>1) Sponsors' study in development<br>2) Dr. Jeffery will present work to validate the algorithm using claims and medical record data from Optum |
| Study of opioid tolerance prevalence lacked data from pre-REMS period, did not evaluate change | Dr. Fleischman's presentation will include pre- and post-REMS data |

# Development of study of overdose risk, opioid non-tolerant vs. opioid-tolerant

- November 2016: Given opioid tolerance was estimated at 58%, FDA asked Sponsors to study adverse outcomes in opioid non-tolerant patients
- December 2017: FDA requested a protocol for study of risk of fatal and non-fatal opioid overdoses among patients who were starting TIRF medicines by opioid tolerance status

# Overdose study development status: July 2018

- Sponsors developing study protocol in parallel with validating opioid tolerance algorithm
- Sponsors have submitted:
  - Feasibility assessment identifying 4 healthcare databases, each linked to cause-of-death data
  - Preliminary count data to help estimate the sample size needed (from 1 database so far; expected from other 3)

# Healthcare databases identified

| Database | Type of Data | Date Range | Number of opioid-non-tolerant TIRF initiators (estimated) |
|---|---|---|---|
| Optum® Clinformatics® | Pharmacy and Medical Claims;<br>Subset of data have linked EMR (Integrated Optum Claims) | 2012-2017 | 600 |
| Allscripts Practice Fusion | Ambulatory care EMR | 2015- 2017 | 689 |
| IBM Watson Health™ MarketScan® | Pharmacy and Medical Claims | 2010-2017 | 1478 |
| IBM Watson Health™ Explorys® | EMR | 2015- 2017 | 400 |

*Total est. ~3,100*

**Sponsor-generated analysis**

EMR, electronic medical record

# Discussion: Development of study of overdose risk by opioid tolerance status

| Key challenges | Potential ways to address challenges |
|---|---|
| Extent of misclassification of exposure (opioid tolerance algorithm) | If opioid tolerance algorithm has poor validity, use medical record data? |
| Extent of misclassification of overdoses identified from medical claims codes | Sensitivity analysis restricted to overdoses identified from death certificates? |
| Potential confounding | Multivariable adjustment methods |
| Small sample size | Assess the expected statistical precision in 4 databases |

# Objective 1
# Conclusions from FDA review (1)

- 58% of patients who start a TIRF medicine are opioid tolerant, as determined by claims-based algorithm
  - 42% are non-tolerant
- This is concerning, and FDA sought more information
- FAERS reports lacked the information we needed
  - No definitive conclusions can be made about these cases

# Objective 1
# Conclusions from FDA review (2)

- FDA directed Sponsors to validate opioid tolerance algorithm
  - Protocol submitted and under review
- Still need information about the overdose risk in opioid non-tolerant patients prescribed TIRF medicines
  - Expecting protocol at end of September 2018

# TIRF REMS goals and objectives

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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.

# Objective 2
# Preventing inappropriate conversion between TIRF medicines

**1. Sponsors' submission**

– Persistency analysis of TIRF utilization

**2. Conclusions from FDA's review**

# Objective 2
# Sponsors' submission

- Preliminary data requested by FDA
  - How many patients are at risk of inappropriate conversion (i.e., changed TIRF therapy)?
  - Preliminary to evaluation of REMS' effectiveness at preventing inappropriate TIRF medicine conversions

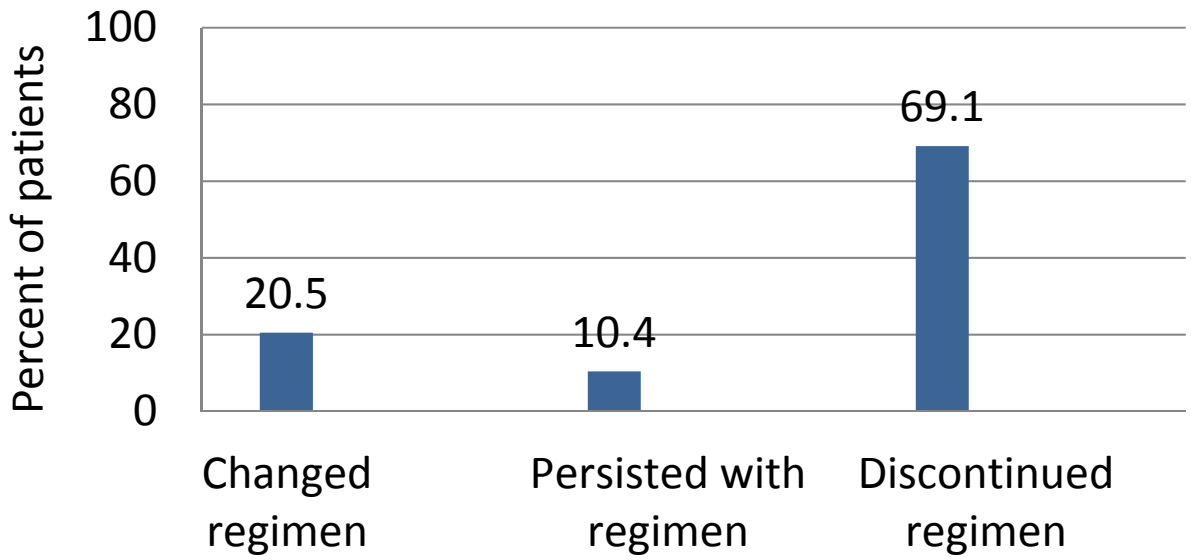
# Persistency analysis of TIRF utilization

- Described utilization of index TIRF regimen
- Estimated the percent of patients who changed, persisted, and discontinued (mutually-exclusive) among 18,160 patients who received ≥2 TIRF dispensings, March 2012 – October 2015
  - Used database from pharmacy management system

# TIRF medicines are "PRN" – How to tell when patient discontinued?

- No standard for permissible gap between TIRF dispensings
  - Can be estimated
- Sponsors conducted exploratory analysis
  - Identified cut-off value to define a permissible gap
  - Beyond permissible gap, considered to have discontinued

# Utilization of TIRF Index Regimen




Population: 18,160 U.S. patients dispensed ≥2 TIRF prescriptions, March 2012 – October 2015.

Data source: TIRF REMS Pharmacy Management System

**Sponsor-generated analysis**

**Outcome:** ***Changed****, dispensed different TIRF med before permissible gap ended;* ***Persisted****, dispensed same TIRF med before permissible gap ended;* ***Discontinued****, no further TIRF dispensing by the end of the permissible gap*

# Objective 2
# Conclusions from FDA review (1)

- Switching TIRF therapy occurred in 20% of patients who filled ≥2 prescriptions over 12-42 months during 2012-2015
- General estimate of population at risk for inappropriate conversions

# Objective 2
# Conclusions from FDA review (2)

- Limitations
  - Results based on medicines dispensed, unclear if consumed
  - May not generalize to patients today, as data collected 3-6 years ago

# Objective 2
# Conclusions from FDA review (3)

- Next step is for Sponsors to estimate prevalence of <u>inappropriate</u> conversions, trend over time
  - Include TIRF medicine dosing instructions and other clinical details
  - May investigate patient outcomes after switching
- FDA expects a protocol submission from the Sponsors

# TIRF REMS goals and objectives

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:

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

# Objective 3
# Preventing accidental exposures

**1. Sponsors' submission**
- Calls to poison centers (TIRF medicines in aggregate)
- Spontaneous adverse event reports

**2. FDA-generated analysis**
- FDA Adverse Event Reporting System (FAERS)
- National Poison Data System (specific TIRF medicines)

**3. Sponsors' new studies in development**
- Studies of accidental poisonings in children

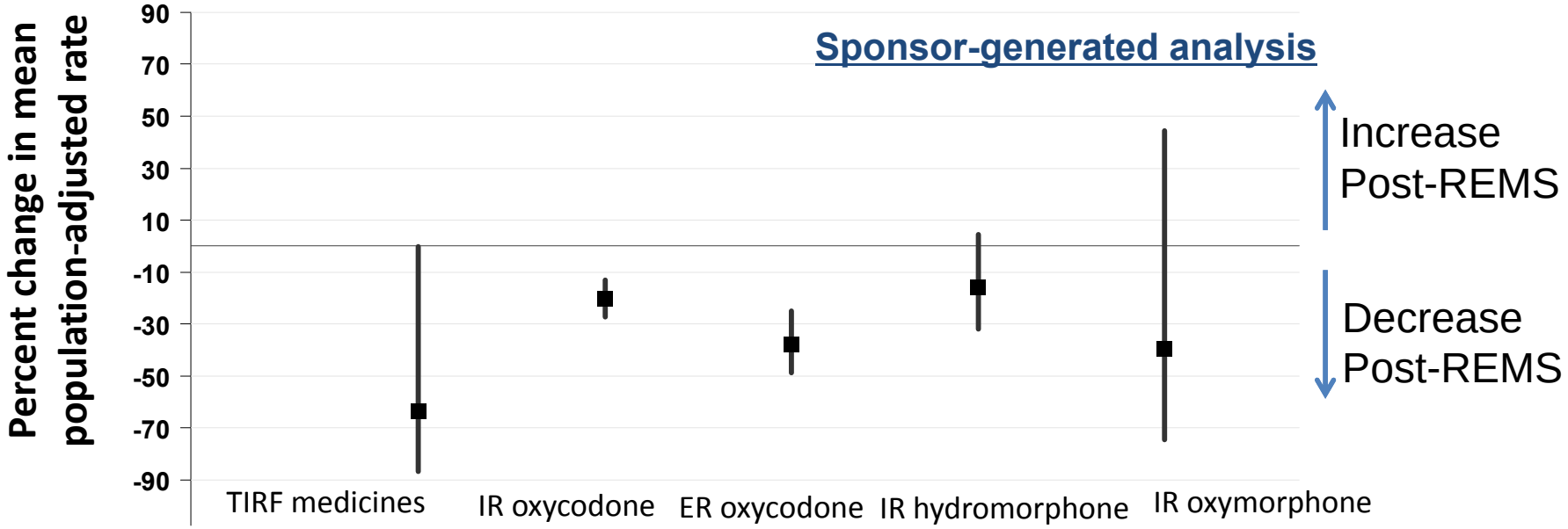
**4. Conclusions from FDA's review**

# Objective 3
# Sponsors' submission

# Sponsors' submission
# Analysis options for AE surveillance data

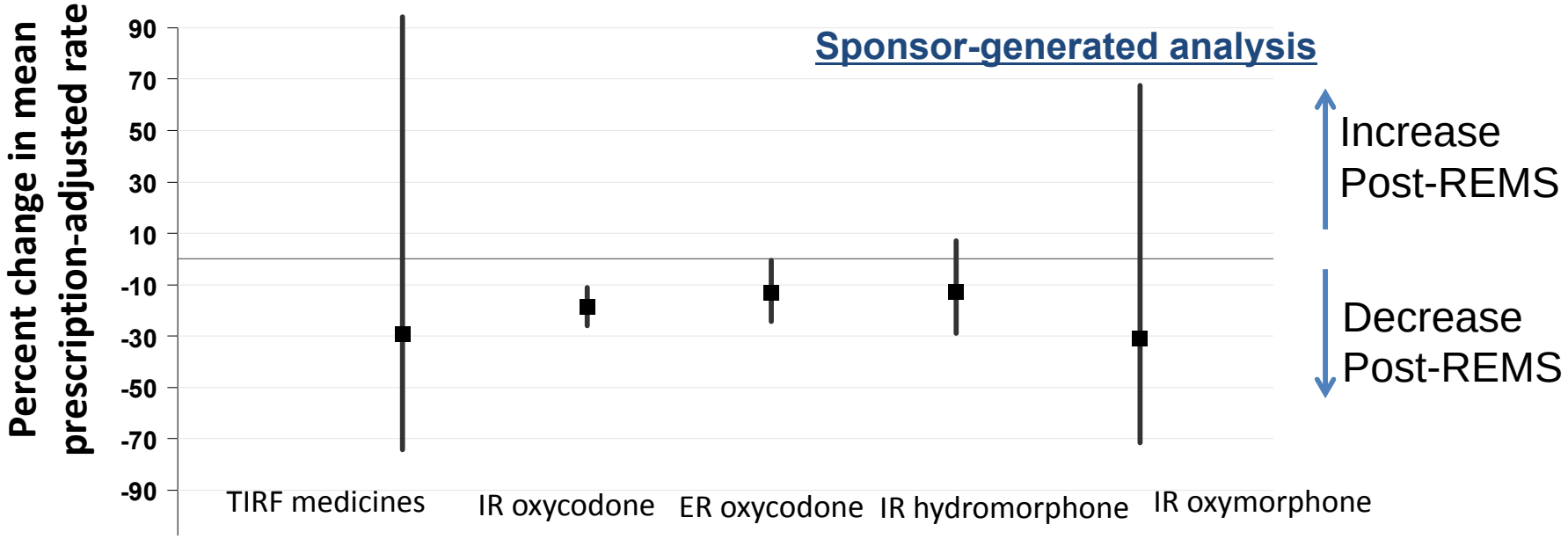
| AE rate denominator | Strengths | Limitations |
|---|---|---|
| **Rate per 100,000 population, population-adjusted** | Reflects the scope of the AE burden, esp. relative to other opioids | Our data sources do not capture all AEs, so cannot measure incidence<br>As TIRF utilization declines, expect decline in pop-adj rate |
| **Rate per 10,000 prescriptions dispensed, prescription-adjusted** | Reflects the potential for harm from prescribing TIRF | In this situation with utilization that is low and in decline, prescription-adj rate, trend are potentially less reliable |

# Poison center data: change in mean population-adj rate of **accidental exposure**




**Outcome:** **Poison center call for "Unintentional general exposure" to any TIRF medicine, or comparator opioid**
**Population:** **Persons seeking medical advice from participating U.S. poison control centers (covering ~90% pop)**
**Source:** **RADARS® Poison Center Program**

# Poison center data: change in mean prescription-adj rate of **accidental exposure**

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**Source:** **RADARS® Poison Center Program**

# Objective 3
# FDA-generated analyses

# FAERS cases of accidental exposure to TIRFs (N=13*)

| | |
|---|---|
| **Cardiac disorders**<br>Palpitations† (1) | **Nervous system disorders**<br>Somnolence (3 pediatric), Syncope (2), Dizziness (1) |
| **Eye disorders**<br>Eye irritation† (1) | **Psychiatric disorders**<br>Euphoric mood (reported as euphoria) (1), Catatonia† (1), Mental status changes (1) |
| **Gastrointestinal disorders**<br>Lip ulceration† (1), Nausea (1), Vomiting (2) | **Respiratory, thoracic, and mediastinal disorders**<br>Respiratory depression (1), Dyspnoea (1 pediatric) |
| **General disorders and administration site conditions**<br>Burning sensation (2), Application site pain† (1), Application site injury (1), Discomfort† (1), Feeling jittery (1), Hyperhidrosis (1), Malaise (1), Pain (1), Flushing (2) | **Skin and subcutaneous tissue disorders**<br>Erythema† (1) |
| **Injury, poisoning and procedural complications**<br>Scratch† (reported as scratch in throat) (1) | **Vascular disorders**<br>Circulatory collapse† (1) |
| **Investigations**<br>Heart rate irregular† (1) | ***A case may report more than one adverse event.**<br>**† Unlabeled adverse event.**<br>**Pediatric adverse events occurred pre-REMS and are boxed.** |

**Received by FDA from January 1, 2010 to December 31, 2017** FDA-generated analysis

# Accidental exposures in young children National Poison Data System

- Found no deaths or major medical outcomes
- Five calls in 2 years pre-REMS (Jul 2010-Jun 2012)
- Five calls in 5 years post-REMS (Jul 2012-Jun 2017)
- Most calls involved Actiq or generic fentanyl citrate lozenge, except one for Subsys exposure

**Outcome:** TIRF medicine exposure by a child age 0 – 6 years, reason "unintentional general"
**Population:** People seeking medical advice from any U.S. poison control center
**FDA-generated analysis**

# Objective 3
# Sponsors' new studies in development

# Further studies of accidental poisonings in children

- Fatal overdoses are under-ascertained by poison centers[1,2], and to an extent that varies by toxin[1,2]
- March 2017: FDA requested that the Sponsors complement their poison center surveillance data with data from EMR, ED and other healthcare claims, and death certificates, to capture the childhood poisonings with severe outcomes

[1]Soslow and Woolf. American Journal of Emergency Medicine 1992.
[2]Hoppe-Roberts et al. Annals of Emergency Medicine 2000. [doi: 10.1067/mem.2000.105932]

# Sponsors' new studies in development

Have started studies of accidental poisonings in children 0 – 6 years using:

1. Healthcare claims linked to medical records (2015-2017)
2. Data mined from the literal text of death certificates (2010-2014)

Also assessed feasibility of Nationwide Emergency Department Sample

# Objective 3
# Conclusions from FDA review (1)

- Accidental childhood poisoning remains a safety concern
  - Incomplete ascertainment of cases possible
  - Poison center data suggest post-REMS decrease in rates, but may miss most severe cases
  - Small number of accidental exposures in adults and children reported to FAERS

# Objective 3
# Conclusions from FDA review (2)

- FDA has recommended enhancing the rigor of surveillance
- Outcome may be too rare to estimate change over time
- Sponsors are undertaking two new studies
  - Death certificate literal text (under FDA review)
  - Medical records with claims linkage (FDA expecting submission of protocol)

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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.

# Goals of mitigating abuse, misuse, overdose…

**1. Sponsors' submission**

- RADARS Poison Center Program
- RADARS Treatment Center Program (TIRF medicines in aggregate)

**2. FDA-generated analyses**

- RADARS Treatment Center Programs (specific TIRF medicines)
- AAPCC* National Poison Data System
- Inflexxion NAVIPPRO treatment center data
- Social media search

**3. Conclusions from FDA's review**

*AAPCC, American Association of Poison Control Centers

# Outcomes and data sources

**FDA-generated analyses**

| OUTCOME | RADARS Poison Center Program (Aggregate TIRF meds) | RADARS Treatment Center | | AAPCC National Poison Data System (Specific TIRF meds) | Inflexxion NAVIPPRO (Specific TIRF meds) | Social Media Search (Specific TIRF meds) |
|---|---|---|---|---|---|---|
| | | Aggregate TIRF meds | Specific TIRF meds | | | |
| Abuse | ■ | ■ | ■ | □ | □ | ● |
| Misuse | ■ | | | □ | | |
| Overdose | ■ | | | ■ | | |
| Medication errors | ■ | | | □ | | |

■ Reviewed and included in presentation; □ Reviewed but not included in presentation; ● Not in background package

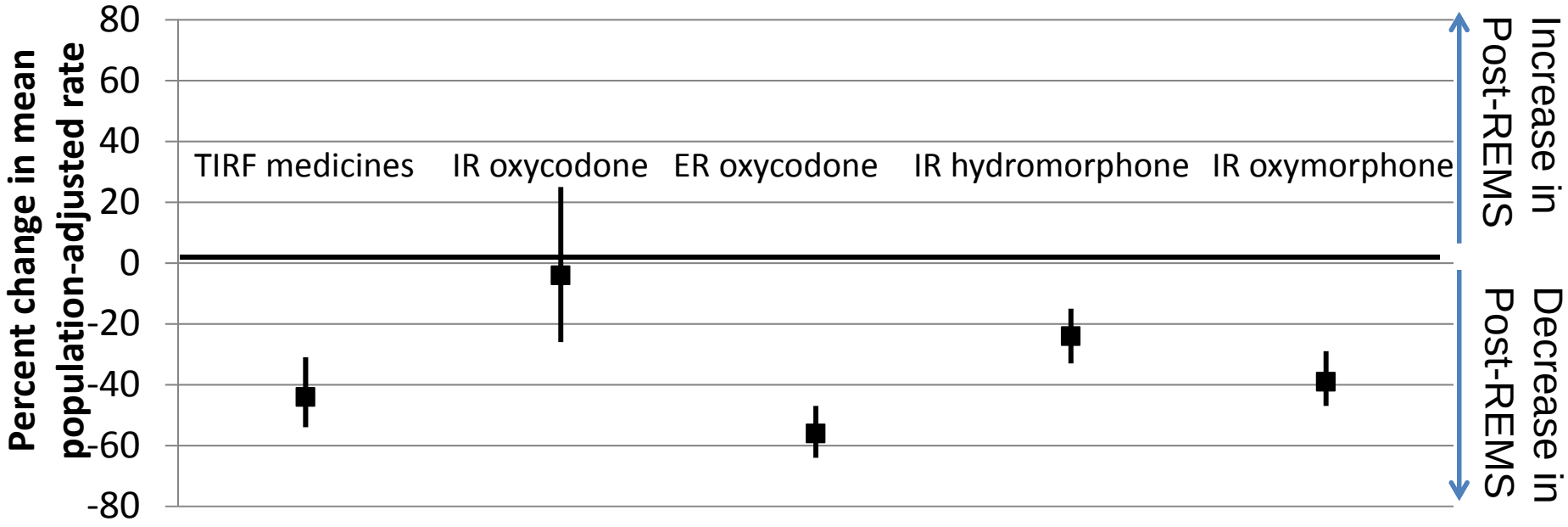
AAPCC, American Association of Poison Control Centers; NAVIPPRO, Nat'l Addictions Vigilance Intervention and Prevention Program: RADARS. Researched Abuse Diversion and Addiction-Related Surveillance

# Goals of
# mitigating abuse, misuse, overdose…
# Sponsors' submission

# Sponsors' submission
# Surveillance data on abuse of TIRF meds

| | RADARS Treatment Center Program | RADARS Poison Center Program |
|---|---|---|
| Population | U.S. adults starting an opioid addiction treatment program | People calling U.S. poison control centers (cover ~90% U.S.) to seek medical advice for a drug exposure |
| Data collection | Respondents fill in survey to select the specific brand and generic prescription drugs they abused in past 30 days | Trained personnel ask caller for details: exposure, reason, product name from container |
| Data on illicit fentanyl? | Survey item before TIRF meds: *fentanyl, unknown form*<br>After: *fentanyl, solution for injection* | Data entry differentiates TIRF medicine from *illicit fentanyl* or simply, *fentanyl* |

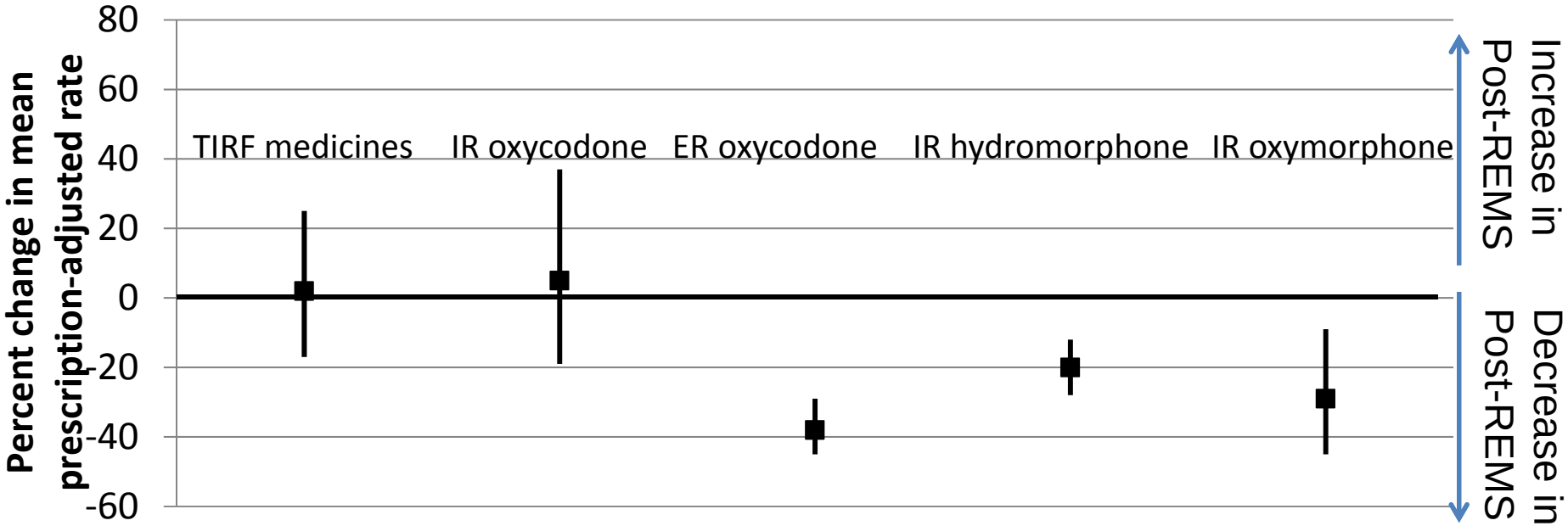
# **Treatment center data**: change in mean **population-adjusted** abuse rate




**Sponsor-generated analysis**

**Outcome:** self-reported abuse of any TIRF medicine, or comparator opioid, past 30 d
**Population:** U.S. adults starting an opioid addiction treatment program at a privately- or publicly-funded center
**Source:** RADARS® Treatment Center Program

# **Treatment center data**: change in mean **prescription-adjusted** abuse rate

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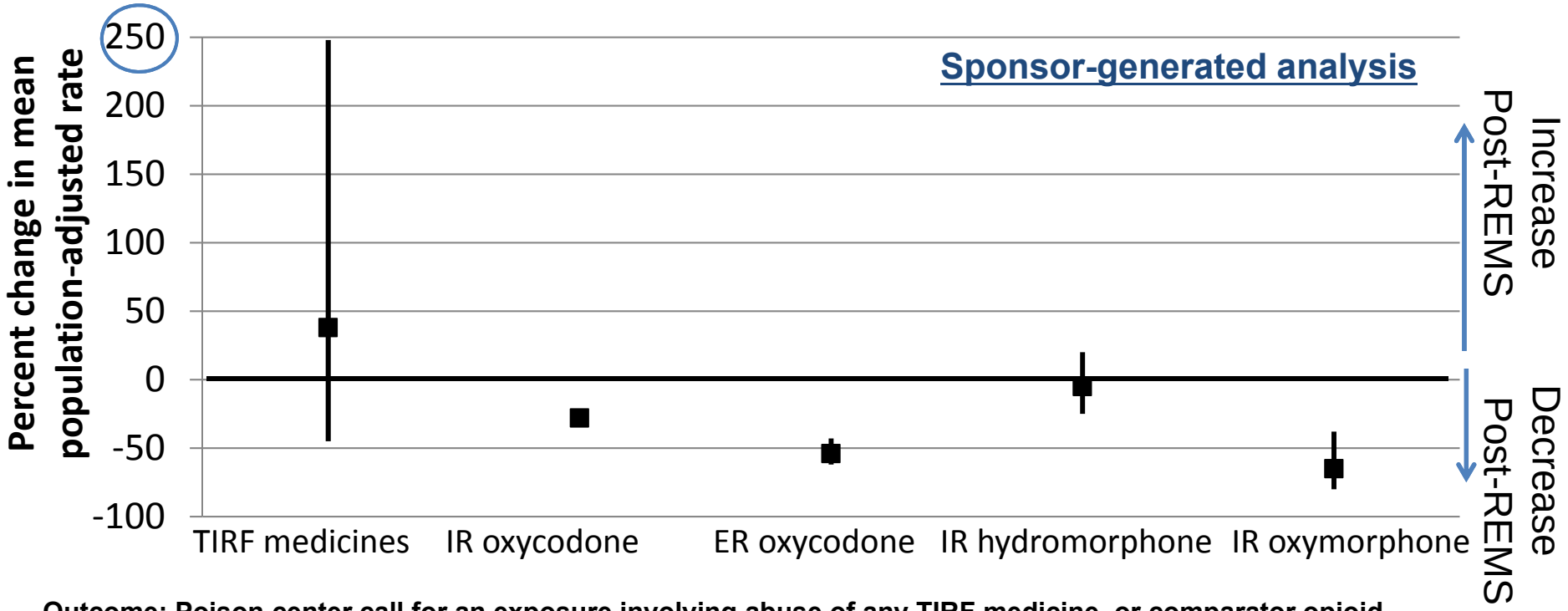
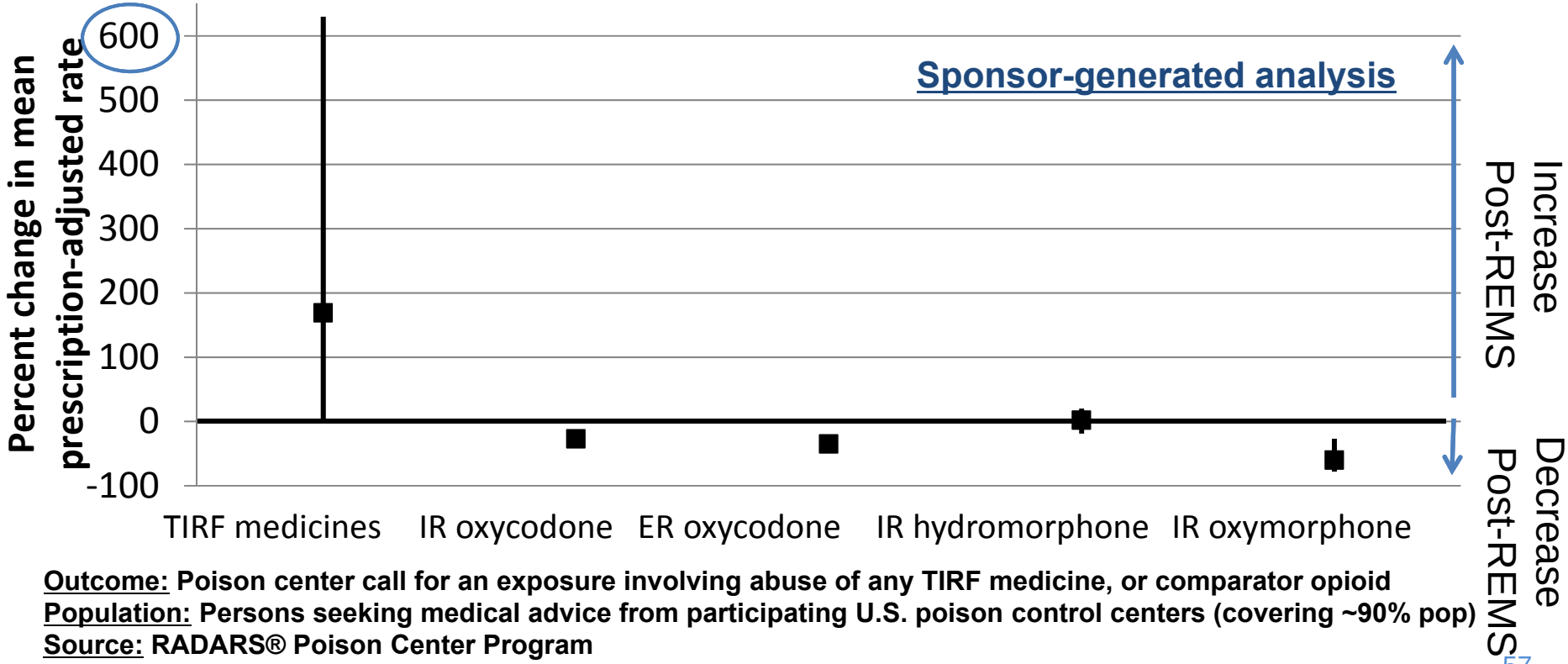
**Outcome:** self-reported abuse of any TIRF medicine, or comparator opioid, past 30 d
**Population:** U.S. adults starting an opioid addiction treatment program at a privately- or publicly-funded center
**Source:** RADARS® Treatment Center Program

# **Poison center data**: change in mean **population-adjusted** abuse rate




**Outcome:** Poison center call for an exposure involving abuse of any TIRF medicine, or comparator opioid
**Population:** Persons seeking medical advice from participating U.S. poison control centers (covering ~90% pop)
**Source:** RADARS® Poison Center Program

# **Poison center data**: change in mean **prescription-adjusted** abuse rate

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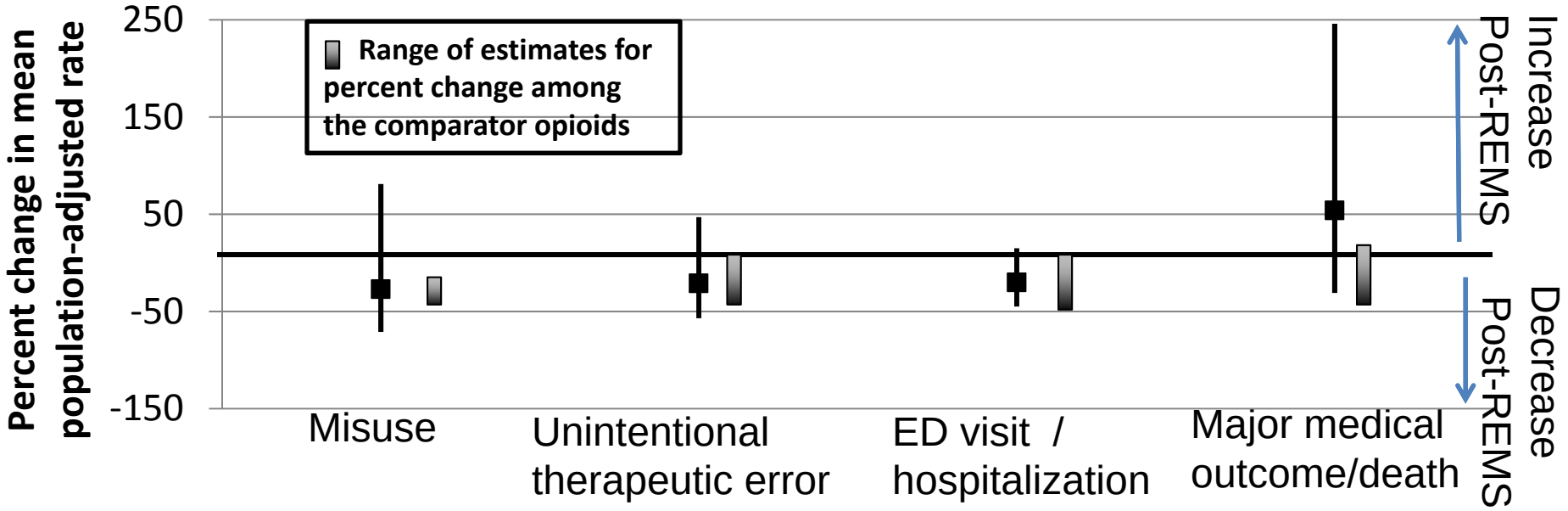
**Population:** **Persons seeking medical advice from participating U.S. poison control centers (covering ~90% pop)**
**Source:** **RADARS® Poison Center Program**

# Poison center data: population-adj rate

## calls involving TIRF medicine exposure

**Sponsor-generated analysis**

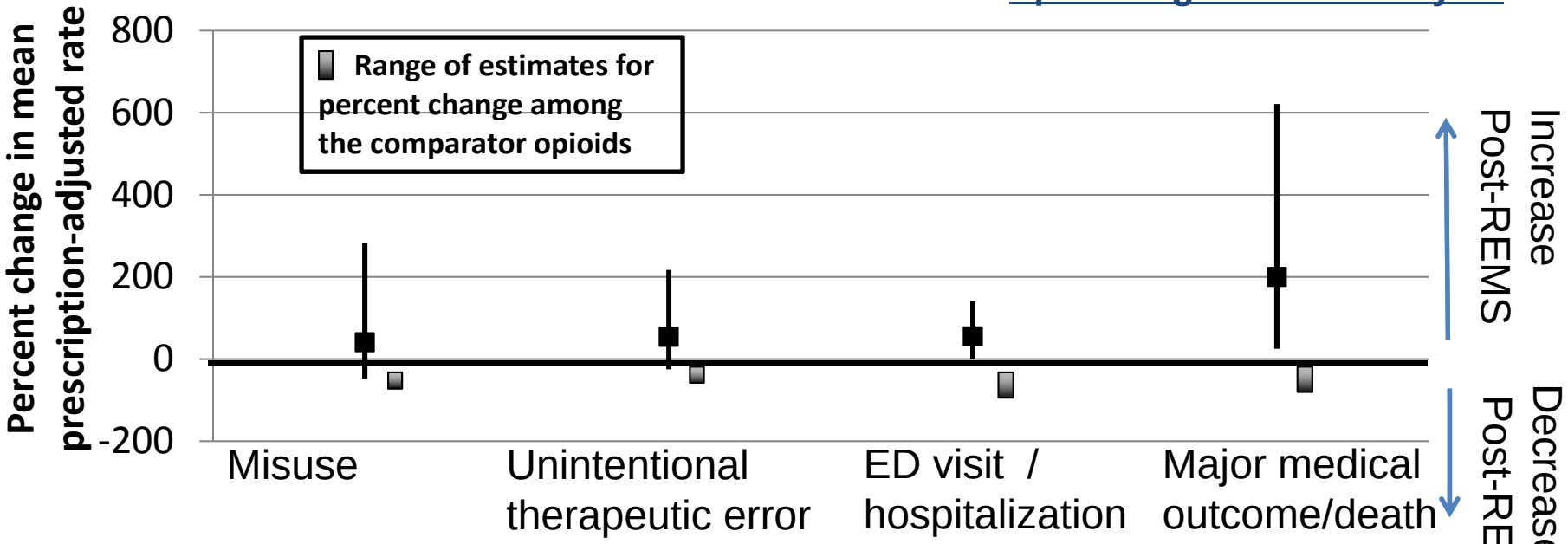



**Outcome:** Poison center call for an exposure due to any TIRF medicine
**Population:** Persons seeking medical advice from participating U.S. poison control centers (covering ~90% pop)
**Source:** RADARS® Poison Center Program

# Poison center data: prescription-adj rate

## calls involving TIRF medicine exposure

**Sponsor-generated analysis**




**Outcome:** Poison center call for an exposure to any TIRF medicine
**Population:** Persons seeking medical advice from participating U.S. poison control centers (covering ~90% pop)
**Source:** RADARS® Poison Center Program

# Goals of
# mitigating abuse, misuse, overdose…
# FDA-generated analyses

# Rationale for FDA additional analyses

- Enable review of TIRF medicines results in aggregate and by product
  - Prior data suggested pre- to post-REMS increases
  - Closer look at broad patterns and discrepancies
  - Some TIRF medicines not marketed pre-REMS

# Poison Center exposure calls resulting in emergency dept visits/hospitalizations

| | Period | Count, n | Percent change in mean prescription-adj rate (95% CI) |
|---|---|---|---|
| Actiq or generic lozenge | Pre-REMS | 28 | reference |
| | Post-REMS | 43 | 68 (4, 170) |
| Fentora | Pre-REMS | 4 | reference |
| | Post-REMS | 7 | 59 (-53, 444) |

**Note:** Abstral, Lazanda, Onsolis, and Subsys could not be analyzed due to sparse data.
**Outcome:** exposure call that involved the drug of interest and resulted in either (1) an admittance to a critical care unit, a noncritical care unit, or a psychiatric care facility, or (2) resulted in treatment or evaluation & release.
**Population:** persons seeking medical advice from any U.S. poison control center, Jul 2010-Jun 2017
**Source:** National Poison Data System **FDA-generated analysis**

# Limitations to comparison of means for REMS evaluation

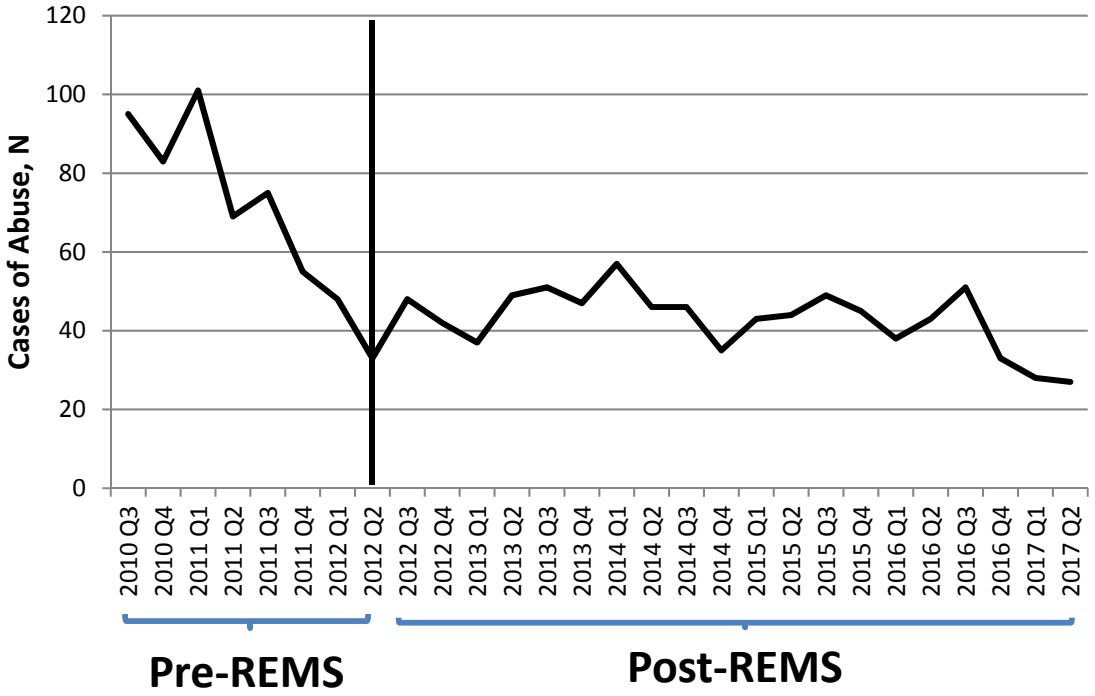
- In pre-REMS (2010-12) & post-REMS (2012-17), **trends** in:
  - TIRF medicine prescribing
  - Opioid prescribing
  - Opioid abuse and overdose

  } Potential influences of **trends** in TIRF abuse?

- Mean is a single, summary measure → can lose information

# Recent abuse of TIRF medicines: Trends pre- and post-REMS

# Cases of TIRF medicine abuse



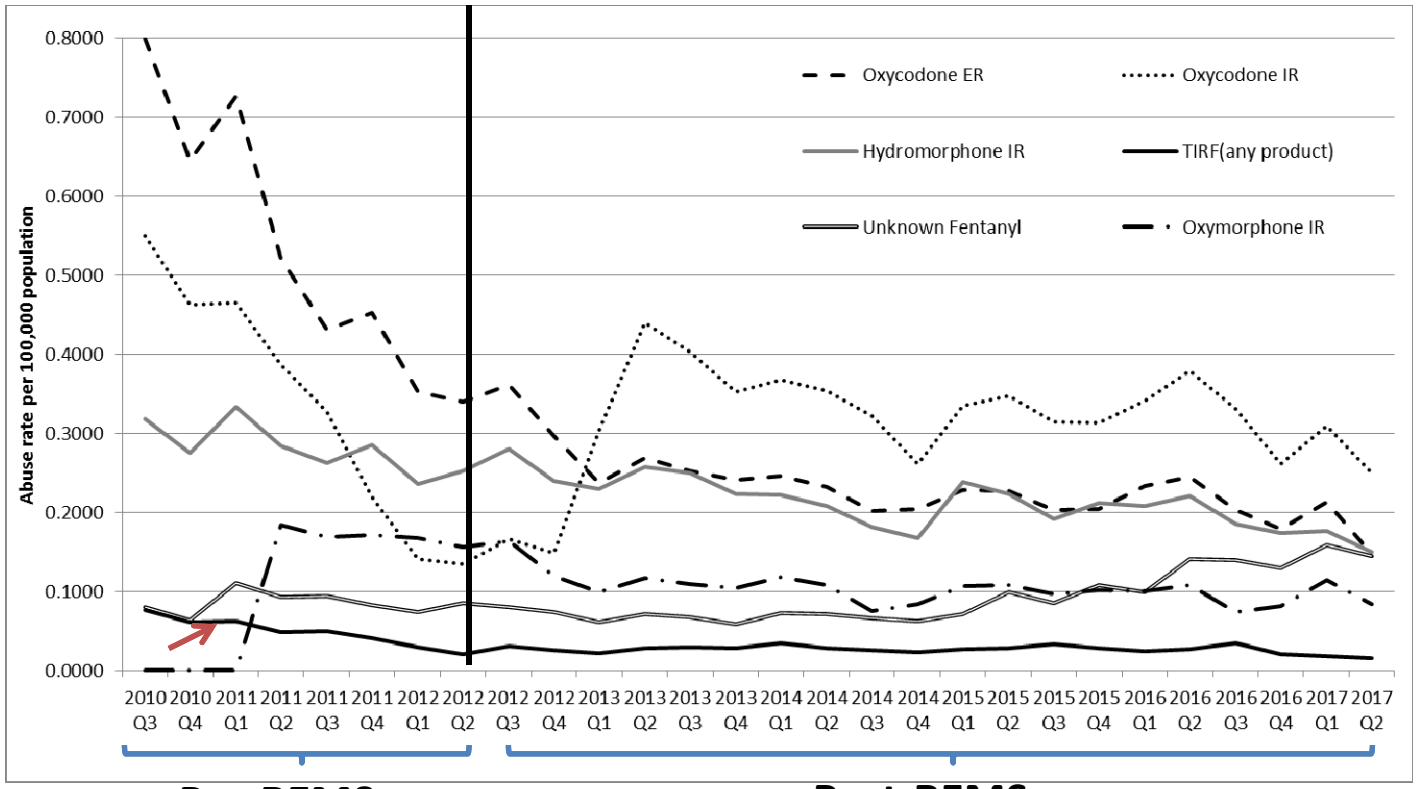

**Outcome:** self-reported abuse of any TIRF medicine, past 30 d

**Population:** U.S. adults starting an opioid addiction treatment program at a privately- or publicly-funded center

**Source:** RADARS® Treatment Center Program

**FDA-generated analysis**

# Population-adjusted abuse rates




**Outcome:** Self-reported abuse of any TIRF medicine, or comparator opioid, past 30 d

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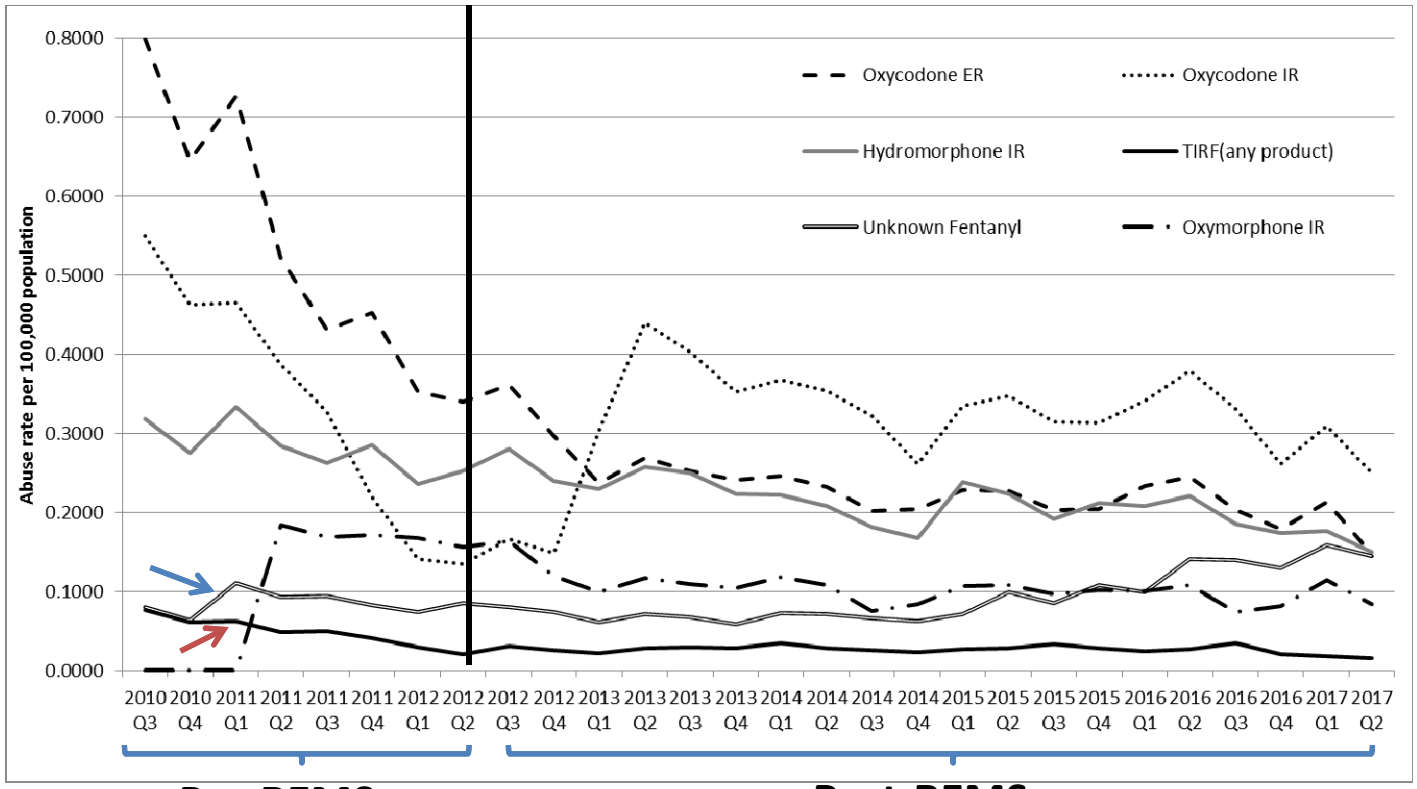
# Population-adjusted abuse rates

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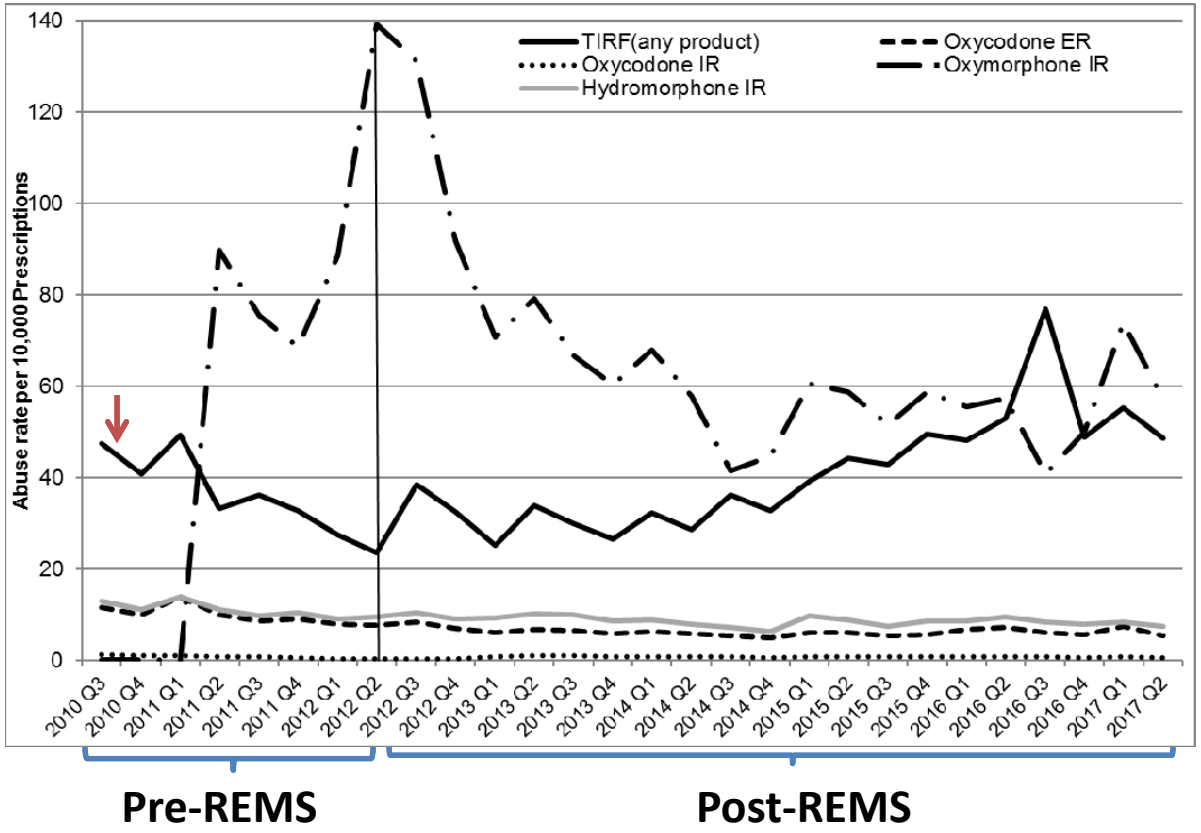
# Prescription-adjusted abuse rates




**Note:**
**A Prescription-adjusted abuse rate cannot be calculated for unknown fentanyl**

**Outcome: Self-reported abuse of any TIRF medicine, or comparator opioid, past 30 d**

**Population: U.S. adults starting an opioid addiction treatment program at a privately- or publicly-funded center**

**Source: RADARS® Treatment Center Program**

**FDA-generated analysis**

# New findings from RADARS Treatment Center Program

- FDA followed up on reasons for abuse patterns observed
- RADARS examined their data:
  - Found no clustering by place, time
  - Late-breaking results showed response patterns suggesting survey respondent “careless reporting” that substantially affects the results of low-volume products
    - Ongoing, FDA-funded research on quality of reporting of abuse of specific products
    - Used tools from survey methodology literature

# New findings from RADARS Treatment Center Program

Methods used to identify response patterns suggesting careless reporting (checking off items indiscriminately):

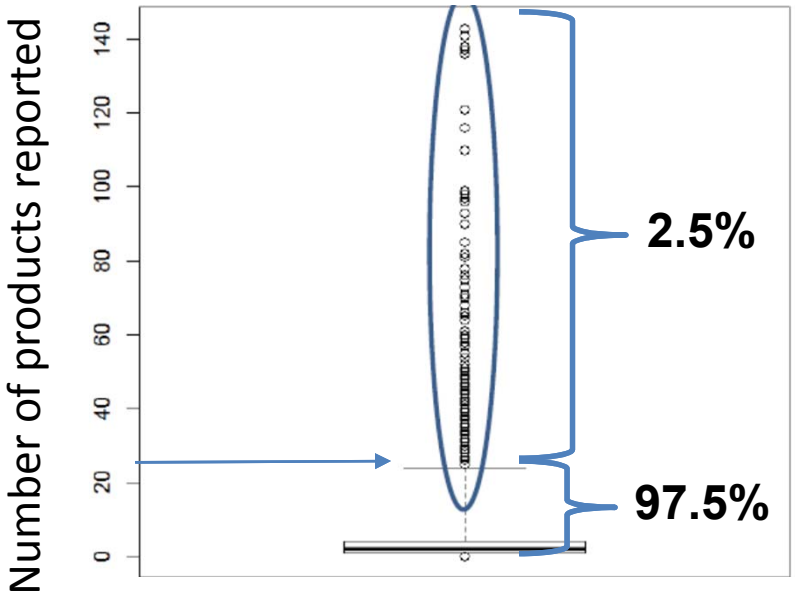
- Outlier analysis
  - Respondent selected large number of items[1]
- Modified *LongString* analysis
  - Respondent selected large number of items in a row[2]
  - High degree of overlap with outlier analysis

[1] Meade and Craig. Psychological Methods 2012. [doi: 10.1037/a0028085]
[2] Johnson. Journal of Research in Personality 2005. [doi: 10.1016/j.jrp.2004.09.009]

# Careless reporting:
# Outlier analysis definition

**Adjusted boxplot:**

**Surveys with ≥1 drug reported, 2017**




- 2.5% of respondents reported recent abuse of **≥ 25** specific products
- Among surveys that reported abuse of a TIRF medicine, median is **22**
- Nearly half of reports of TIRF medicine abuse may be due to careless reporting

Outcome: self-reported abuse of any opioid product, past 30 d
Population: U.S. adults starting an opioid addiction treatment program at a privately- or publicly-funded center, 2017
Source: RADARS® Treatment Center Program **FDA-generated analysis**

# RADARS Treatment Center Program: Conclusions

- These late-breaking findings mean a substantial proportion of Treatment Center Program reports of TIRF medicine abuse may be unreliable
- RADARS will update drug abuse surveillance results
- FDA expects the small number of cases will be even smaller

# Data sources for abuse: Other important limitations

- Treatment centers
  - Findings may not generalize to all people who abuse drugs, or who seek treatment
- Poison centers
  - Under-ascertainment of exposures with severe outcomes (i.e., death)
  - Under-ascertainment of exposures may vary over time and by toxin

# Social media search

- Search: each TIRF medicine, pre- and post-REMS
  - Themes in the social media posts?
  - Mentions of counterfeit TIRF medicines?
  - Qualitative changes in the discussion over time?
- Found: postings related to abuse of each TIRF med
  - No mentions of counterfeit TIRF meds
  - No qualitative trends in discussion

# Goals of mitigating abuse, misuse, overdose…Conclusions from FDA review (1)

- Concerned about increases in rates of poison center calls:
  - Abuse of TIRF medicines (24 events)
  - Major medical outcomes/deaths attributed to TIRF medicine exposure (21 events)
- Relatively few reports of abuse in treatment center data
  - Late-breaking findings from RADARS suggest careless reporting by respondents affected the TIRF medicines results
  - FDA is expecting updated results

# Goals of mitigating abuse, misuse, overdose…Conclusions from FDA review (2)

- Observed few events, but suggestive increases in prescription-adjusted rates of poison center calls:
  - Unintentional therapeutic errors (35 events)
  - Misuse (18 events)
  - Exposures resulting in ED visits/hospitalizations (102 events)
- Thus, these results are difficult to interpret

# TIRF REMS goals and objectives

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.

# Summary conclusions (1)

**Objective 1: Ensuring use in appropriate patients**

- 58% of patients starting TIRFs are opioid non-tolerant. FDA is concerned and has directed the Sponsors to undertake further studies to understand associated outcomes and algorithm validity.
- FAERS data are inconclusive.

**Objective 2: Preventing inappropriate conversions**

- 20% of patients with ≥2 TIRF dispensings change regimen and are at risk for inappropriate conversions. FDA is expecting a protocol for a study of inappropriate conversions.

# Summary conclusions (2)

**Objective 3: preventing accidental exposures**

- Poison center call rates declined. To capture the most severe cases, Sponsors are undertaking additional studies of accidental childhood poisoning.

**Goals of mitigating abuse, misuse, overdose, …**

- Suggestive increases in rates of select AEs observed, though based on few events.

# Acknowledgments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# FDA Concluding Remarks

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

August 3, 2018

Doris Auth, Pharm.D.

Associate Director

DRISK/OMEPRM/OSE/CDER

# TIRF medicines are potent, rapidly-acting opioid analgesics

- TIRF REMS was required to address:
  - the potential for significant respiratory depression and death in:
    - patients that are not opioid-tolerant
    - individuals, particularly children, who may accidentally ingest these products
  - the potential for medication errors and adverse outcomes associated with inappropriate conversions between TIRF products
  - the risks of abuse, misuse, and overdose with these products

# TIRF REMS Key Components

- TIRF REMS was designed to address these risks with minimal burden on the healthcare delivery system and patient access, through:
  - Education of prescribers and pharmacists
  - Counseling patients on risks and safe use practices
  - Ensuring enrolled prescribers prescribe to patients who have completed a PPAF

# TIRF REMS Assessment Findings

- TIRF REMS has been implemented and continues to operate as intended
- Overall utilization and enrollment declining
- Overall knowledge of risks and safe use high for most risk messages
- Use in non opioid-tolerant patients concerning
- Outcome measures have been challenging to obtain; results show some concerning findings

# TIRF REMS Assessment Gaps

- Impact of declining utilization and prescriber enrollment on appropriate patient access?
- Reasons that prescribers and pharmacies are not re-enrolling?
- Validity of opioid tolerance algorithm?
- The best methods for studying:
  - Overdose events in non opioid-tolerant vs opioid-tolerant?
  - Accidental poisonings in children?
  - Abuse and misuse data considering recent RADARS findings?


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