FDA Introductory Remarks

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Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

May 3-4, 2016

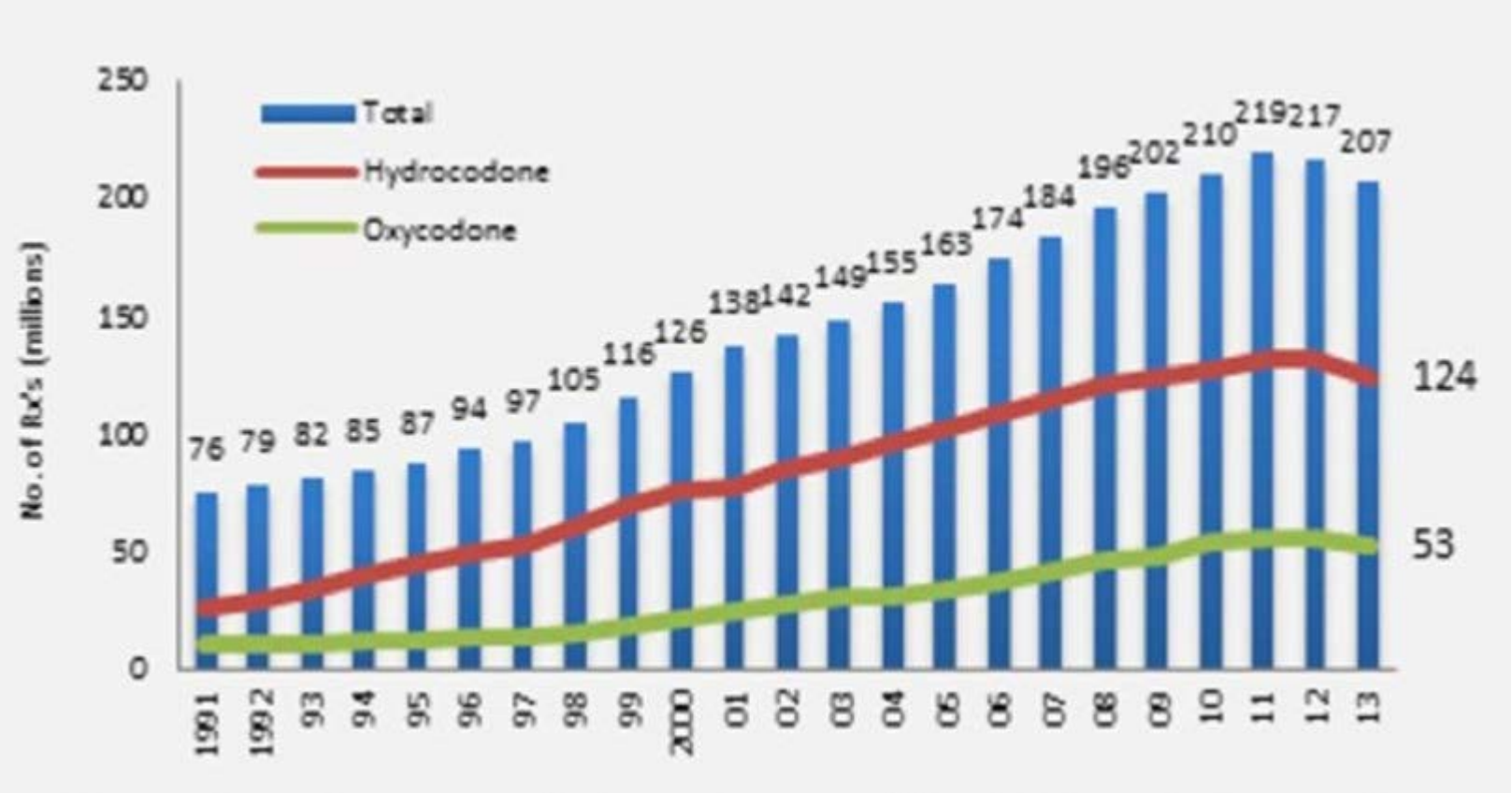
Current State

- US experiencing a devastating epidemic of prescription opioid misuse and abuse, including a large number of overdose deaths
- Expert opinion finds that the treatment of pain in the US, particularly chronic pain, is not satisfactory, including an over-reliance on prescription opioids (2011 IOM Report)
- The Science and data needed to inform policy implementation are often lacking

This is Not Our First Opioid Epidemic

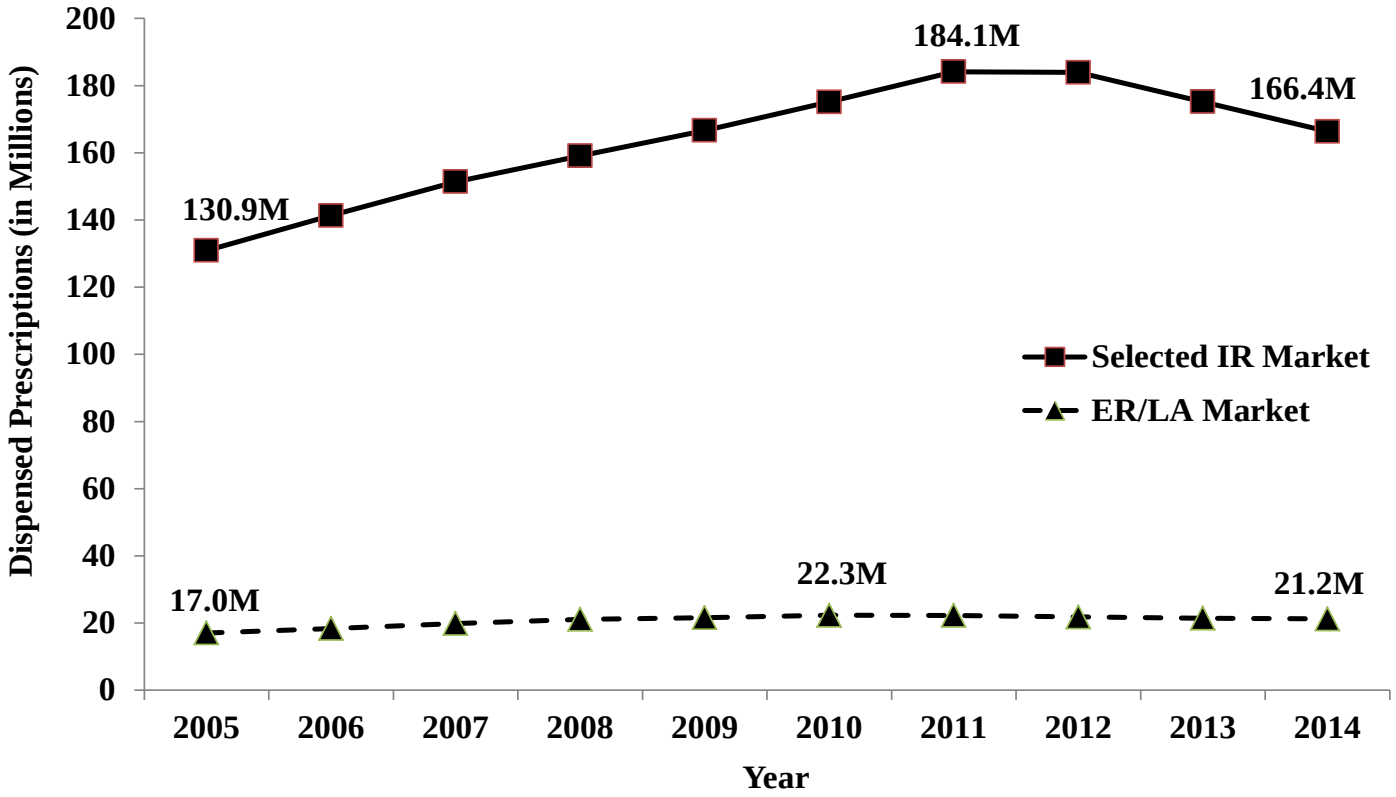
1860s	Addiction epidemic due to over-prescribing of morphine and laudanum in patent medicines
1960s	Heroin epidemic led to federal "War on Drugs"
1990s	JCAHO issued guidelines—pain to be considered the "5th Vital Sign"
1990-2000	Additional opioid molecules and formulations developed and marketed, including higher-potency ER/LA formulations; practitioners responded with ever-increasing prescribing.
2000s	FDA modifies label of OxyContin based on reports of abuse and diversion, including boxed warnings; initiates a risk management plan in 2001.
2000-2010	Opioid prescribing continues to escalate. "Pill mills" proliferate.

Prescriptions for Opioid Analgesics Dispensed by US Retail Pharmacies



From: **https://www.drugabuse.gov/**about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse

National Estimates of Prescriptions Dispensed for Selected *IR and ER/LA Opioid Analgesics from U.S. Retail Pharmacies



Source: IMS Health, National Prescription Audit™. Extracted May and August 2015
*Selected IR Opioids include: Hydrocodone combination analgesics (hydrocodone with acetaminophen, ibuprofen or aspirin), Oxycodone combination analgesics (oxycodone with acetaminophen, ibuprofen or aspirin), oxycodone IR, hydromorphone IR, morphine IR, tapentadol IR, and oxymorphone IR.

Patterns of Opioid Analgesic Use (2002-2014)

- FDA analyzed a large sample of more than half of all outpatient retail prescriptions in US
- Over 176 million patients included in study
- Among patients with at least one episode of chronic opioid analgesic use (≥ 90 days):
  - About 12 million patients had a chronic episode of only IR opioid analgesic use
  - About 3 million patients had a chronic episode of only ER/LA opioid analgesic use

IMS Health, Data Extract Tool, 2002-2014

Appropriate Management of Acute Pain in the Outpatient Setting

- Trauma, post-surgery, ruptured disc, etc
- Alternative armamentarium is limited, primarily NSAIDS or acetaminophen
- NSAIDs have well-known serious side effects, may not be appropriate where bleeding is a concern
- Combination hydrocodone/acetaminophen and oxycodone/acetaminophen most popular
- Major issue is # of tablets/duration of RX
  - Many people don't take/can't tolerate
  - Leads to large excess sitting in medicine cabinets across the country
  - Disposal practices must be improved, but better not to dispense so many to start with

Appropriate Management of Chronic Non-cancer Pain

- Physicians have been urged for 20 years to more aggressively respond to a patient's pain
- But chronic pain is not a single, simple entity
- Most physicians not trained in the currently recommended multimodal approach
- Resources (insurance coverage, other providers) may not be available
- Patient education is time-consuming
- Prescription drug products available and often covered by health insurance

Use of Opioid Medications in Healthcare Settings

- Hospital use: anesthesia; surgery and post-surgical care; trauma and burn care; palliative care; cancer; terminal illness
- Outpatient surgical, dental and other procedures
- Nursing homes: palliative care, terminal illnesses
- Rehab hospitals
- Hospice care
- Outpatient acute pain—emergency departments, post-surgery, physician's offices, etc.
- Outpatient cancer pain
- Outpatient chronic non-cancer pain—the most controversial area
- **Each of the above has legitimate uses for opioids**

Alternatives to Opioid Analgesics

- Pharmacologic
  - NSAIDs
  - Acetaminophen
  - Anticonvulsants
  - Antidepressants
  - Local Anesthetics
  - Others (e.g. capsaicin, ziconotide)
  - Disease-Modifying Antirheumatic Drugs (DMARDs)
  - Newer pharmacologic therapies

- Non-pharmacologic
  - Cognitive behavioral therapy
  - Physical therapy
  - Surgical
  - Better treatment of underlying disease
  - Alternative medicine (e.g., accupuncture)

Pharmacologic Alternatives: Safety Concerns

Analgesics

NSAIDS

Boxed warnings:

- **Cardiovascular**
- **Gastrointestinal**

Others:

renal, hepatic, hypertension, CHF, anaphylactoid, anemia, platelet inhibition, skin reactions, Premature closing of ductus arteriosis; bronchospasm in aspirin-sensitive asthma

ACETAMINOPHEN

Warnings:

- **Severe liver damage**
- **Allergic reaction**
- **Skin (potentially fatal)**

Antidepressants

DULOXETINE

Suicidal Thoughts and Behaviors, Hepatotoxicity - hepatic failure, Orthostatic Hypotension, Falls and Syncope, Serotonin Syndrome, Abnormal Bleeding, Severe Skin Reactions, Angle-Closure Glaucoma, Seizures, Hypertension, Hyponatremia, Glucose Control in Diabetes, Urinary Hesitation and Retention

MILNACIPRAN

Suicidality, Serotonin Syndrome, Elevated blood pressure and heart rate, Seizures, Hepatotoxicity, Abnormal Bleeding, Worsened Dysuria, Angle Closure Glaucoma

Anticonvulsants

PREGABALIN

Angioedema, Hypersensitivity, Suicidal Behavior and Ideation, Dizziness and Somnolence, Weight Gain, Tumorigenic Potential, Ophthalmological Effects, Decreased Platelet Count, PR Interval Prolongation

GABAPENTIN

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity, Anaphylaxis and Angioedema, Effects on Driving and Operating Heavy Machinery, Somnolence/Dizziness

CARBAMAZEPINE

Serious Skin Reactions, Hypersensitivity, Aplastic Anemia, DRESS, Suicidal Behavior and Ideation

Other

LIDOCAINE TOPICAL PATCH

Accidental pediatric exposure, allergy/anaphylaxis, lidocaine toxicity

CAPSAICIN

Eye and mucous membrane irritation, pulmonary irritation, application site pain and increased blood pressure

ZICONOTIDE

Cognitive and neuropsychiatric adverse reactions (confusion, memory impairment, hallucinations), meningitis, CNS depression, elevated creatinine kinase

POTENTIAL NEW THERAPIES

Unknown

Challenge

- Best approach to reduce overall population exposure to opioids while retaining appropriate pain management in the various care settings

FDA Approach

- Prevention of abuse and addiction
  - **Prescriber education (ER/LA REMS);** updated labels
  - Better data on longer-term use of opioids for pain (required studies)
  - Development of standards for abuse-deterrent formulations
  - Development of alternative pain therapies
  - Improved disposal practices (with Federal and State agencies)
- Prevention of OD deaths: naloxone
- Treatment of Addiction: Medication Assisted Therapy
- Summarized in recent Action Plan

Advisory Committee Discussion and Meeting Objectives

- Obtain the Committees' views on the ER/LA Opioid Analgesic REMS
  - Discuss the current REMS program
  - Consider whether the REMS program is achieving goals
  - Consider whether any modifications should be made to the REMS program, or whether the program should remain the same or be eliminated

Discuss ER/LA Opioid Analgesic REMS

- Should the REMS be modified?
  - Should the content of the current blueprint be expanded?
  - Are the current Medication Guide and Patient Counseling Document appropriate?
  - Is a REMS for the IR opioid analgesics necessary to ensure the benefits outweigh the risks?
  - Should prescribers be required to complete training in order to prescribe opioid analgesics through a closed restricted distribution REMS or through other mechanisms?
  - Others?

Development of the 2012 Extended Release and Long-Acting (ER/LA) Opioid Analgesic REMS

Terry Toigo
Associate Director, Drug Safety Operations
Center for Drug Evaluation and Research

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

May 3-4, 2016

Overview

2000 - 2009	FDA Risk Management Activities prior to the ER/LA REMS
2009 - 2011	ER/LA REMS Development Activities
2012	ER/LA REMS Approval

Extended Release and Long Acting Opioid Analgesic REMS = Opioid REMS = ER/LA Opioid REMS = ER/LA REMS

Risk Management Activities

2000

FDA first received reports of significant problems with prescription opioid abuse, especially involving OxyContin.

- crushing of the tablet to defeat the extended-release (ER) properties
- misuse by several different routes
- addiction, overdose and death

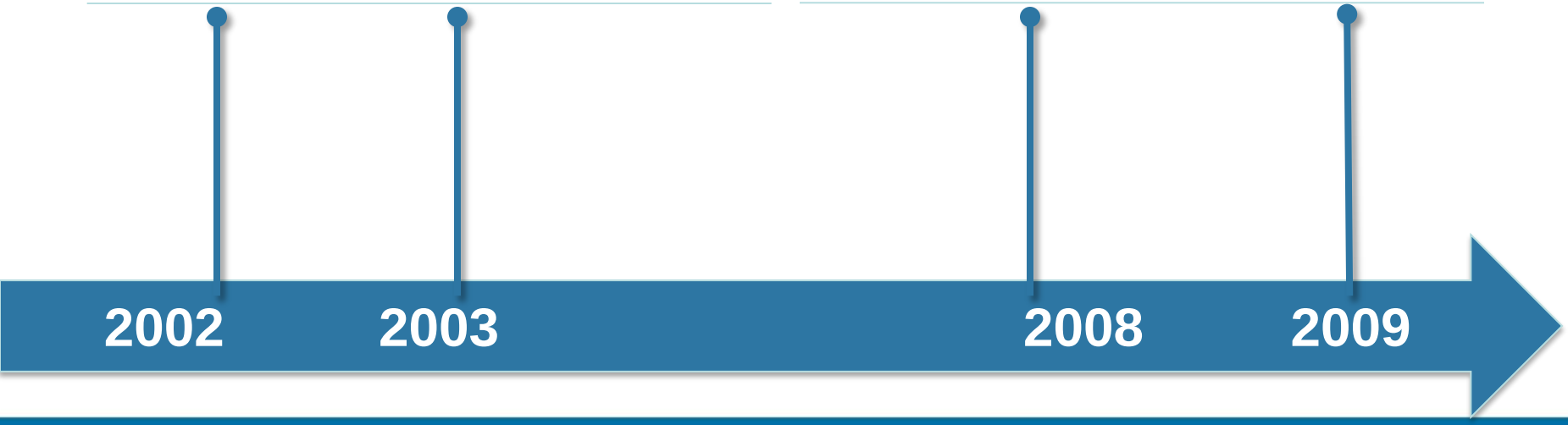
2001

Risk Management Plan (RMP) for OxyContin

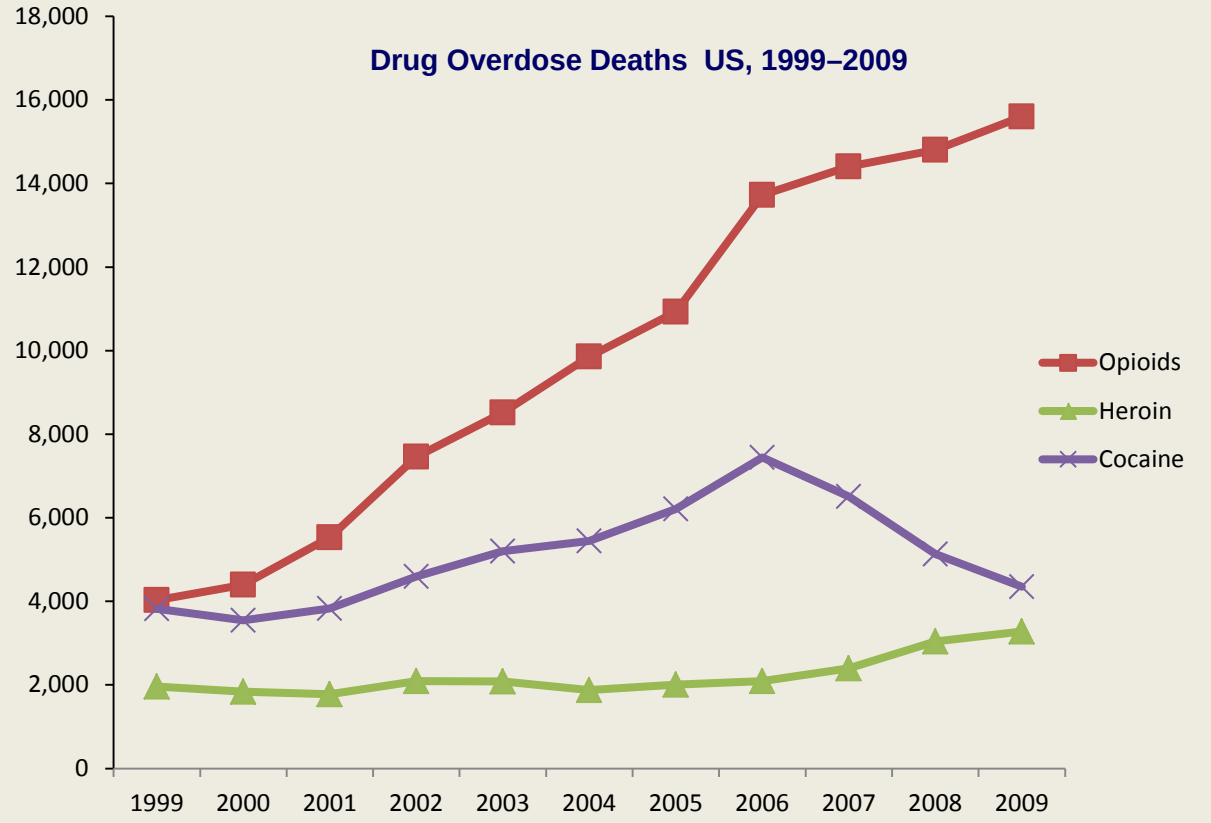
- Labeling Changes, including Boxed Warning
- Education to health care professionals, surveillance, and intervention when a signal of misuse or abuse became apparent

Advisory Committee Meetings

Meetings of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)



Opioid Deaths Continue to Rise 1999–2009



Source: National Vital Statistics System

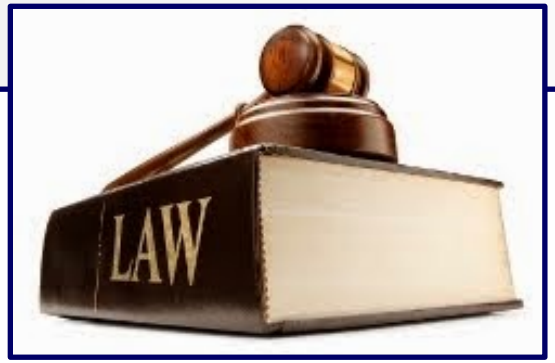
Despite adding warnings to product labeling and developing RMPs to prevent inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics–

Drug overdose deaths resulting from opioids continued to increase.

New Safety Authorities for FDA

Food and Drug Administration Amendments Act of 2007
Public Law 110-85 *(September 27, 2007)*

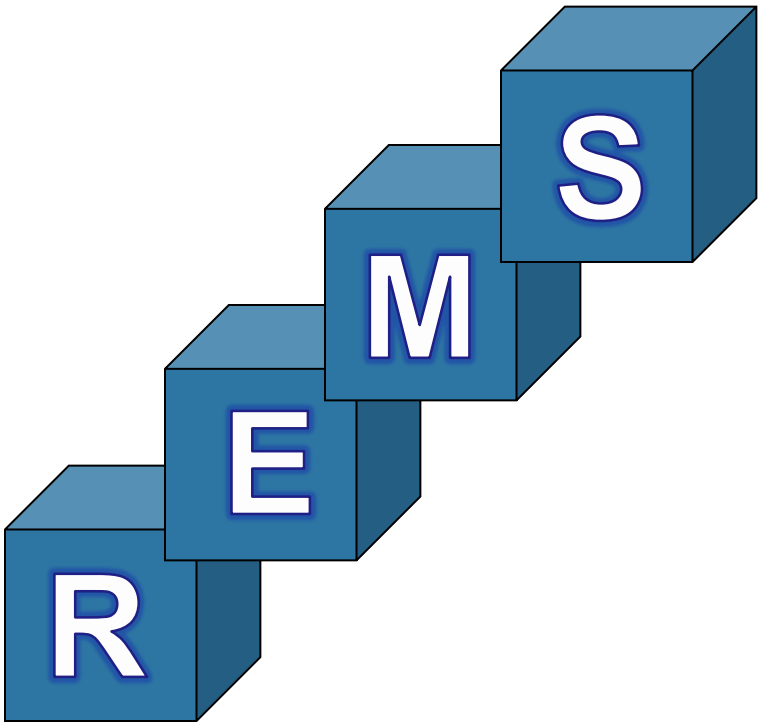
Contents:
Title I: Prescription Drug User Fee Amendments of 2007
Title II: Medical Device User Fee Amendments of 2007
Title III: Pediatric Medical Device Safety and Improvement Act of 2007
Title IV: Pediatric Research Equity Act of 2007
Title V: Best Pharmaceuticals for Children Act of 2007
Title VI: Reagan-Udall Foundation
Title VII: Conflicts of Interest
Title VIII: Clinical Trial Databases
Title IX: Enhanced Authorities Regarding Postmarket Safety of Drugs
Title X: Food Safety
Title XI: Other Provisions



FDA Amendments Act of 2007 (FDAAA), Title IX gave FDA three new safety authorities:

- Authority to require a REMS under section 505-1
- Authority to require safety labeling changes (SLC) under section 505(o)(4)
- Authority to require postmarketing studies and clinical trials (PMRs) under section 505(o)(3)

FDA Informs Sponsors a REMS is Needed



February 6, 2009

FDA notified holders of ER/LA opioid analgesics that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks.

March 3, 2009

FDA met with the application holders to discuss the REMS design to manage the risks while considering the burden on the health care system.

2009

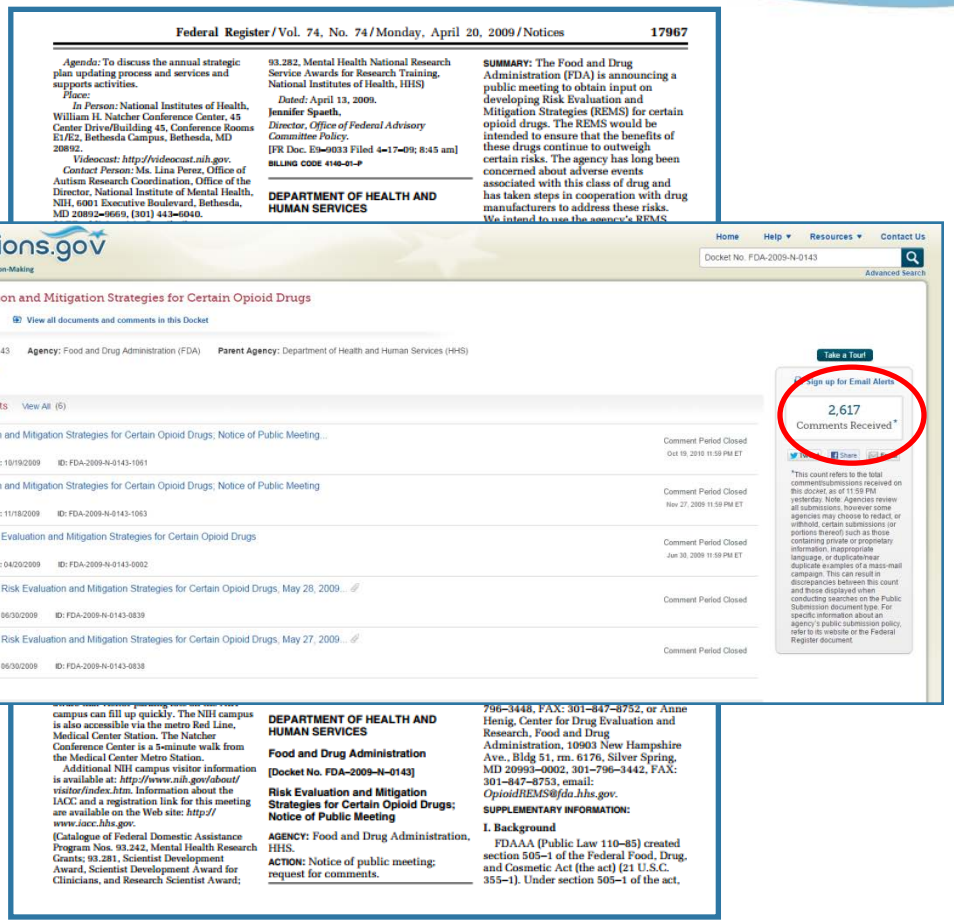
Stakeholder Input: Public Docket

FDA opened a public docket on April 20, 2009.

FDA is interested in obtaining information and public comment on the following issues:

a. Elements of the REMS
b. System Issues

FDA received 2617 comments on the proposed REMS.



Federal Register / Vol. 74, No. 74 / Monday, April 20, 2009 / Notices 17967

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2009–N–0143]

Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting to obtain input on developing Risk Evaluation and Mitigation Strategies (REMS) for certain opioid drugs. The REMS would be intended to ensure that the benefits of these drugs continue to outweigh certain risks. The agency has long been concerned about adverse events associated with this class of drug and has taken steps in cooperation with drug manufacturers to address these risks.

regulations.gov
Your Voice in Federal Decision-Making

Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs

Docket Folder Summary | View all documents and comments in this Docket

Docket ID: FDA-2009-N-0143 Agency: Food and Drug Administration (FDA) Parent Agency: Department of Health and Human Services (HHS)

Primary Documents View All (6)

Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting...
Notice Posted: 10/19/2009 ID: FDA-2009-N-0143-1061 Comment Period Closed

Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting
Notice Posted: 11/18/2009 ID: FDA-2009-N-0143-1063 Comment Period Closed

Meetings: Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs
Notice Posted: 04/20/2009 ID: FDA-2009-N-0143-0002 Comment Period Closed

Public Meeting Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs, May 28, 2009...
Other Posted: 06/30/2009 ID: FDA-2009-N-0143-0839 Comment Period Closed

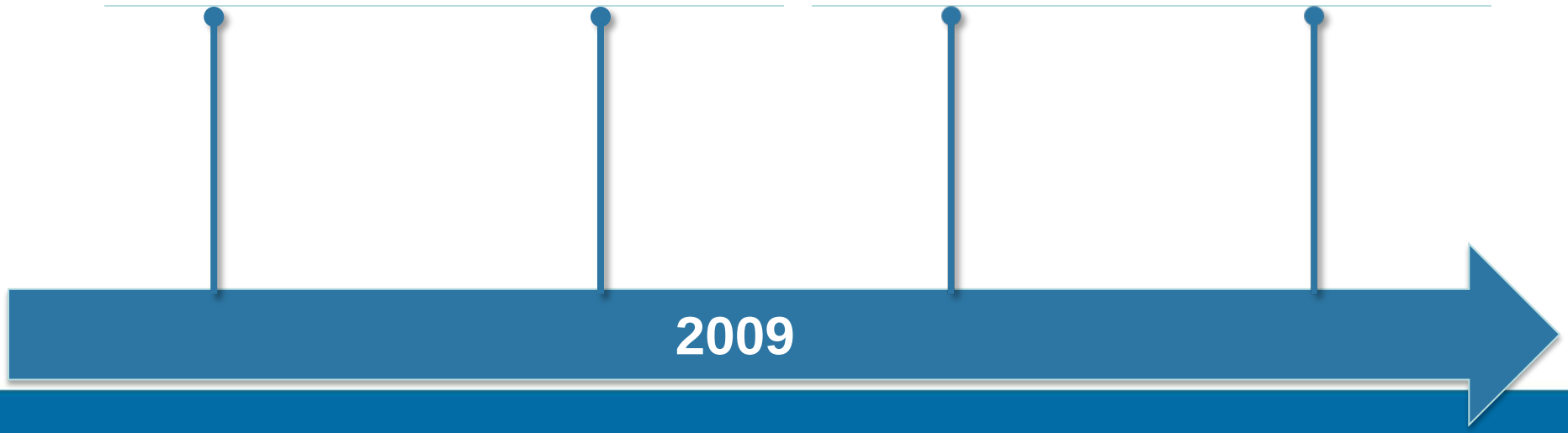
Public Meeting Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs, May 27, 2009...
Other Posted: 06/30/2009 ID: FDA-2009-N-0143-0838 Comment Period Closed

2,617 Comments Received*

2009

Stakeholder Input: Public Meetings

February 9, 2009	May 4-5, 2009	May 27-28, 2009	December 4, 2009
Discuss the regulatory process and standards for review and approval of opioid products.	Obtain comments and opinions regarding the development of an opioid REMS	Hear about experiences with opioid drugs and suggestions for a REMS for ER/LA opioid products.	Hear from industry about their views on the specific features of the REMS.

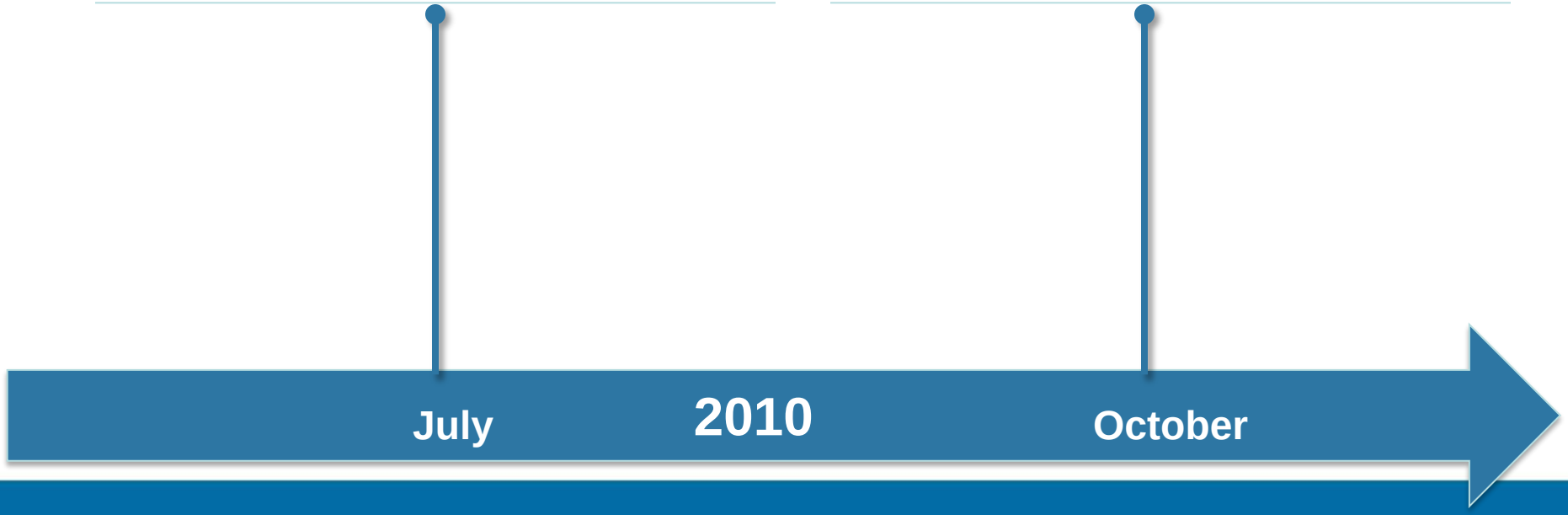


More Advisory Committee Meetings

Joint Meetings of ALSDAC and DSaRM

- Discuss FDA's proposal for a class-wide REMS for ER/LA opioid analgesics and to solicit feedback on the components of the proposal

- Discuss the design of postmarketing studies to assess whether abuse deterrent properties actually result in a decrease in the risks of misuse and abuse, addiction, overdose, and death



Some Considerations in Developing the REMS

1. Scope of the REMS
2. Impact on the Health Care System
3. Impact on Patient Access to the Drug

2011

Some Highlights of Stakeholder Comments (1)

Size Largest and most complex program of its kind

Drugs If the REMS only applies to ER/LA opioids, there will be shifts in prescribing to IR products or other potentially less effective pain relievers. Methadone should have a separate REMS.

Prescriber Education Many comments supported prescriber education but comments were divided as to whether such education should be mandatory.

- Include safe use, storage, and disposal of opioid medications, pain management, benefits and risks of opioid treatment.
- If education is mandated, REMS certification should be linked to DEA registration to maximize participation, minimize cost, and streamline the prescription process.

2011

Some Highlights of Stakeholder Comments (2)

Prescriber Certification	Individual prescriber enrollment and real time verification of prescriber training at pharmacy level could cause "opting out." Consider linking certification to DEA registration or state requirements (e.g. state Medical Board Licensure).
Patient Education and Certification	Patient education is vital to the safe use of REMS drugs. A REMS that employs a patient registration system would be overly burdensome and create a stigma for pain patients that could adversely affect patient access to necessary medications.
Program Evaluation	It is critical to assess the effectiveness of the program and its impact on appropriate access to pain medications.
Other	Less restrictive elements should be implemented first to determine if they are effective in mitigating risk while preserving access.

2011

Balancing Risk, Burden, and Patient Access

ETASU shall be commensurate with the specific serious risk listed in the labeling of the drug and considering such risk,

- Not be unduly burdensome on patient access to the drug
- And to the extent practicable minimize the burden on the health care delivery system

April 19, 2011

FDA sent REMS notification letters to application holders of ER/LA opioid analgesics. The notification letters specified requirements for

- Prescriber training/education
- Assessment plan and timetable for submission of assessments
- Medication Guide
- Patient Education Materials

Focus of the REMS was education and ER/LA products.

2011

Prescriber Education

NDA ######

APPENDIX A: CONTENT OF EDUCATION PROGRAM

The training for prescribers required by the elements to assure safe use must contain the following content:

1. General information for safe opioid prescribing
   a. Patient selection and assessment
      i. Determine goal of therapy
      ii. Assessment of the risk of abuse, including history of substance abuse and serious mental illness
      iii. When relevant, determining if patient is opioid tolerant
   b. Considerations when prescribing opioids
      i. Pharmacokinetics and potential for overdose
      ii. Addiction, abuse, and misuse
      iii. Intentional abuse by patient or household contacts
      iv. Interactions with other medications/substances
   c. Managing patients taking opioids
      i. Establishing goals for treatment and evaluating pain control
      ii. Use of Patient Provider Agreements (PPAs)
      iii. Adherence to a treatment plan
      iv. Recognizing aberrant behavior
      v. Managing adverse events
   d. Initiating and modifying dosing of opioids for chronic pain
      i. As first opioid
      ii. Converting from one opioid to another
         1. Converting from immediate-release to extended-release and long-acting products
         2. Converting from one extended-release and long-acting product to another
      iii. Titrating to effect/tolerability
      iv. How to deal with missed doses

- Prescriber education program includes
  - General information about the use of the class of ER/LA opioid analgesics to aid in patient selection and counseling
  - Specific drug information
  - Information about how to recognize the potential for and evidence of addiction, dependence, and tolerance
  - Training conducted by accredited, independent CME providers
- Training is not mandatory to prescribe ER/LA opioids.
  - FDA supported mandatory training linked to DEA registration as proposed in the Administration's comprehensive plan to address the epidemic of prescription drug abuse in April 2011.

2011

ACCME and FDA Collaboration

- FDA worked with the Accreditation Council for Continuing Medical Education (ACCME) and other accrediting bodies and CE providers.
- Goal was to help ensure that CE programs developed to comply with the REMS would
  - be in compliance with ACCME accreditation criteria and
  - standards for commercial support.

2011

FDA Lessons Learned re: CME

FDA and the CME community had different expectations for *The Blueprint for Prescriber Education*

FDA

- FDA creates a *high level outline* to guide content of the Blueprint.
- FDA expected the *application holders to work together to develop the draft content* for FDA review and approval.
- This is analogous to how we handle the prescribing information in the label, i.e., sponsors may develop the draft, but FDA controls the content.

CME Community

- *FDA would develop the Blueprint* for CE providers to use to develop the actual CE content.
- Application holders provide FDA with information about the scope of the content.
- CME Community wanted to be sure that the FDA "controlled" the content of the professional education.

2011

FDA Blueprint Available for Public Comment

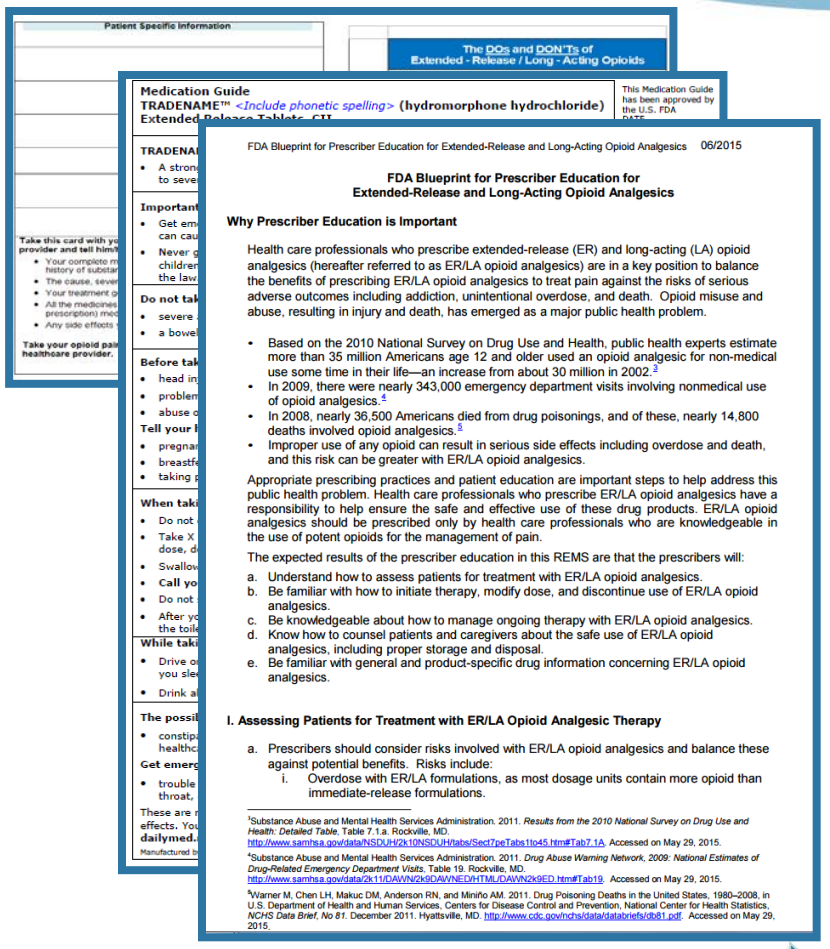
- November 7, 2011 “Blueprint for Prescriber Education for Long-Acting/Extended-Release Opioid Class-Wide REMS”

- FDA received comments from about 65 individuals or organizations.
- Most comments were favorable and offered specific edits.
- The negative comments focused primarily on the REMS being ineffective in addressing the problem because
  - completion of the REMS training by prescribers is voluntary
  - industry is involved
  - the ER/LA opioid analgesic focus is too narrow

2011

REMS Approval

- FDA considered comments received and on July 9, 2012, approved the ER/LA Opioid Analgesics REMS.
- The REMS included a
  - Patient Counseling Document for prescriber to give to patient
  - One-page Medication Guide
- Final FDA “blueprint”
  - Posted on FDA website for accredited CE providers to develop training supported by independent educational grants from ER/LA opioid manufacturers.
  - Content focuses on safe prescribing of ER/LA opioid analgesics.
  - Directed to prescribers of ER/LA opioid analgesics but may be relevant for other healthcare professionals.


Patient Specific Information

The DOs and DON'Ts of Extended - Release / Long - Acting Opioids

Medication Guide
TRADENAME™ <Include phonetic spelling> (hydromorphone hydrochloride)
Extended-Release Tablets, CII

This Medication Guide has been approved by the U.S. FDA

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics 06/2015

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.[3]
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.[4]
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.[5]
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products. ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.

The expected results of the prescriber education in this REMS are that the prescribers will:

a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
   i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

[3]Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A. Accessed on May 29, 2015.

[4]Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD. http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19. Accessed on May 29, 2015.

[5]Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81*. December 2011. Hyattsville, MD. http://www.cdc.gov/nchs/data/databriefs/db81.pdf. Accessed on May 29, 2015.

2012

Summary

The overarching goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

When *developing* the REMS, FDA considered stakeholder input about the scope and impact of the REMS on the health care system and patient access.

When *making modifications* to the REMS, one of the things FDA considers is how proposed changes to the REMS can minimize the burden of implementing the REMS on practitioners, patients, and others in various health care settings.

Risk Evaluation and Mitigation Strategies (REMS) Authority and Extended-Release and Long-Acting (ER/LA) Opioid Analgesic REMS

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Office of Surveillance and Epidemiology

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
May 3-4, 2016

Presentation Outline

- Overview of the Risk Evaluation and Mitigation Strategies (REMS) Authorities
- Extended-release and long-acting (ER/LA) Opioid Analgesic REMS ("ER/LA REMS")
- ER/LA REMS Assessment Plan

Risk Evaluation and Mitigation Strategy (REMS)

- Food and Drug Administration Amendments Act of 2007 (FDAAA) provided FDA the legal authority to require REMS for applicable drugs
- A REMS is a required risk management plan that utilizes risk mitigation strategies beyond FDA-approved professional labeling
- REMS can be required:
  - Pre-approval, if FDA determines a REMS is needed to ensure that the benefits of the drug outweigh the risks
  - Post-approval, if FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks

Components of a REMS

- A REMS can include:
  - Medication Guide or Patient Package Insert (PPI)
  - Communication Plan for Healthcare Providers (HCPs)*
  - Elements to Assure Safe Use (ETASU)
  - Implementation System
- Must include a Timetable for Submission of Assessments of the REMS*

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

Elements to Assure Safe Use (ETASU)

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

ETASU REMS

Restrictive

- **Distribution/dispensing linked to**
  - **certification/training of prescribers,**
  - **certification of pharmacies and/or healthcare settings**
  - **enrollment of patients**
  - **documentation of safe use conditions**

Non-restrictive

- **Application holders required to make training available to likely prescribers**

REMS Training Requirements
2 possible scenarios

- **Training is <u>required</u> in order to prescribe or dispense the drug** *(Restrictive or closed distribution program)*
    - Training is mandatory for prescribers who decide to participate in the program
- **Training is <u>not required</u> in order to prescribe or dispense the drug** (*Non-restrictive program*)
    - Sponsors are required to make training available
    - Participation is voluntary for prescribers, and can be low.

Non-restrictive Program

Training is not required in order prescribe or dispense the drug

Sponsor provides or makes training available.

Prescriber

Completes training

Restrictive or Closed Distribution Program- *REMS requires training*

Sponsor provides training

Prescriber

Completes training

Distributor

Sponsor Database

Pharmacy verification

Completes certification

Patient

ER/LA Opioid Analgesic REMS

ER/LA Opioid Analgesics Included in the REMS

Active ingredients in ER/LA products:

Buprenorphine	Fentanyl	Tapentadol
Hydrocodone	Hydromorphone	Methadone
Morphine	Oxycodone	Oxymorphone

24 Sponsors comprise the ER/LA REMS Product Companies (RPC)

Includes approximately 60 applications (NDA and ANDA)

Goal of the ER/LA REMS

To reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

ER/LA REMS Elements

- Medication Guide
- Elements to Assure Safe Use: **Prescriber Training* via sponsor funded CE guided by the *FDA Blueprint***
- Additional REMS materials include:
  - Patient Counseling Document (PCD)
  - Letters to healthcare professionals
  - REMS website
- Timetable for Submission of Assessment
  - 6 and 12 months post-approval and annually thereafter; components of each assessment change until year 4

*** Prescriber education was the one strategy that was supported by all stakeholders at public meetings**

ER/LA REMS Medication Guide

Medication Guide
TRADENAME™ *<Include phonetic spelling>* **(hydromorphone hydrochloride)**
Extended Release Tablets, CII

This Medication Guide has been approved by the U.S. FDA
DATE

TRADENAME is:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to relieve moderate to severe-around-the-clock pain.

Important information about TRADENAME:
- Get emergency help right away if you take too much TRADENAME (overdose). TRADENAME overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:
- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
- pregnant or planning to become pregnant. TRADENAME may harm your unborn baby.
- breastfeeding. TRADENAME passes into breast milk and may harm your baby.
- taking prescription, over the counter medicines, vitamins, or herbal supplements.

When taking TRADENAME:
- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take X dose at the same time every day. Do not take more than X dose in XX hours. If you miss a dose, do not take TRADENAME. Take your next dose at your usual time the next day.
- Swallow TRADENAME whole. Do not break, chew, crush, dissolve, or inject TRADENAME.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- Do not stop taking TRADENAME without talking to your healthcare provider.
- After you stop taking TRADENAME flush any unused *[insert dosage form i.e. tablet or patch]* down the toilet.

While taking TRADENAME DO NOT:
- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over the counter medicines that contain alcohol.

The possible side effects of TRADENAME are:
- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency help if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: *[insert manufacturers name and address here]*

- 1-page format
- Includes info applicable to all products & product specific info needed for safe use
- Aids patient in use of medication at home
- Intended to be an adjunct to patient counseling, not a replacement

Patient Counseling Document

- Facilitates discussions at the time of prescribing with pt/caregivers.
- One-page document
- Important safety info about all ER/LA opioid analgesics.
- Space to write pt/drug specific information (e.g. name of drug, dose, route of administration)

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics

DO:

- Read the **Medication Guide**
- Take your medicine exactly as prescribed
- Store your medicine away from children and in a safe place
- Flush unused medicine down the toilet
- Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Call 911 or your local emergency service right away if:

- You take too much medicine
- You have trouble breathing, or shortness of breath
- A child has taken this medicine

Talk to your healthcare provider:

- If the dose you are taking does not control your pain
- About any side effects you may be having
- About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements

DON'T:

- **Do not** give your medicine to others
- **Do not** take medicine unless it was prescribed for you
- **Do not** stop taking your medicine without talking to your healthcare provider
- **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- **Do not** drink alcohol while taking this medicine

For additional information on your medicine go to:
dailymed.nlm.nih.gov

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

Patient Specific Information

Take this card with you every time you see your healthcare provider and tell him/her:

- Your complete medical and family history, including any history of substance abuse or mental illness
- The cause, severity, and nature of your pain
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects you may be having

Take your opioid pain medicine exactly as prescribed by your healthcare provider.

ER/LA REMS Prescriber Education via Continuing Education (CE)

- Supported by independent educational grants from ER/LA Sponsors
- Provided through accredited CE providers
- Prescriber training is not a mandatory precondition for prescribing
- Content is not exhaustive nor a substitute for a more comprehensive pain management course
- *FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics* was developed to provide the core messages to be communicated to prescribers through CE

FDA Blueprint for Educational Content

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

III. Managing Therapy with ER/LA Opioid Analgesics

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

V. General Drug Information for ER/LA Opioid Analgesic Products

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

http://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioids_2015-10-23_FDA_Blueprint.pdf

ER/LA REMS-Compliant Training

- Training is provided and offered by an accredited CE provider
- Includes all elements in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
- Includes a knowledge assessment of all of the sections of the FDA Blueprint
- Is subject to independent audit to confirm that conditions of the REMS training have been met

Prescriber Training Targets

320,000 ER/LA prescribers

July 2012: ER/LA REMS Approved with FDA Blueprint

2012

2013

Feb 28, 2013: 1st REMS –Compliant training becomes available

2014

2015

Mar 2015: 1st Training Target: 80,000 Prescribers (25% of total)

36-month REMS Assessment Report July 2015

2016

Mar 2016: 2nd Training Target: 160,000 Prescribers (50% of total)

2017

Mar 2017: 3rd Training Target 192,000 Prescribers (60% of total)

2018

Elements of the ER/LA REMS 36-month Assessment Report

1. Number of ER/LA prescribers who have completed training
2. Independent audit of the quality and content of the educational programs.
3. Prescriber surveys
4. Patient survey
5. Surveillance studies- key safety outcomes
6. Drug utilization patterns
7. Changes in prescribing behavior
8. Evaluation of patient access

Discussion Topics

- What are the expectations for a voluntary education program?
- Are the data sources and methodologies used to evaluate the REMS appropriate?
- Has the REMS had an impact on patient access?
- Is the REMS meeting its goals?
- Does the REMS assure safe use?
- Is the REMS unduly burdensome?
- To the extent possible does the REMS minimize the burden on the healthcare delivery system?

Discussion Topics

continued

- Are the *FDA Blueprint,* Medication Guide and Patient Counseling Document sufficient or are changes needed?
- Should a REMS be required for the immediate release (IR) opioid analgesics to ensure the benefits outweigh the risks?
- Should prescriber training be mandatory in order to prescribe opioid analgesics?

Lastly, consider if the ER/LA REMS should:

- continue without modifications,
- be eliminated,
- be modified and if so how?

Introduction to FDA Reviews of the Extended-Release and Long-Acting (ER/LA) Opioid Analgesic REMS 36-month Assessment

Igor Cerny, Pharm.D.
REMS Assessment Analyst
Division of Risk Management
Center for Drug Evaluation and Research

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM)
& Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

May 3-4, 2016

REMS Goal

- To reduce *serious adverse outcomes* resulting from inappropriate prescribing, misuse, and abuse of ER/LAs while maintaining patient access to pain medications. Adverse outcomes of concern include *addiction*, *unintentional overdose*, and *death*

ER/LA REMS Assessment Plan

1) Number of ER/LA prescribers who have completed training
2) Independent audit of the quality and content of the educational programs.
3) Prescriber surveys
4) Patient survey
5) Surveillance studies- key safety outcomes
6) Drug utilization patterns
7) Changes in prescribing behavior
8) Evaluation of patient access

FDA Presentations to Follow:

Patient and Prescriber Surveys:
Review & Statistical Evaluation
- Shelly Harris, MPH (DRISK/OSE)
- Ya-Hui Hsueh, PhD (DB VII)

Epidemiologic and Drug Utilization Surveillance Studies
- Jana McAninch, MD MPH MS (DEPI II)

Overall FDA Conclusions & Considerations
- Igor Cerny, Pharm.D. (DRISK/OSE)

Prescriber Training Targets

320,000 ER/LA prescribers (FDA estimate 2011)

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36-month REMS Assessment Report July 2015

2016

Feb 29, 2016: 2nd Training Target: 160,000 Prescribers (50% of total)

2017

Feb 28, 2017: 3rd Training Target 192,000 Prescribers (60% of total)

2018

Numbers of RPC-Supported REMS-compliant CE Activities

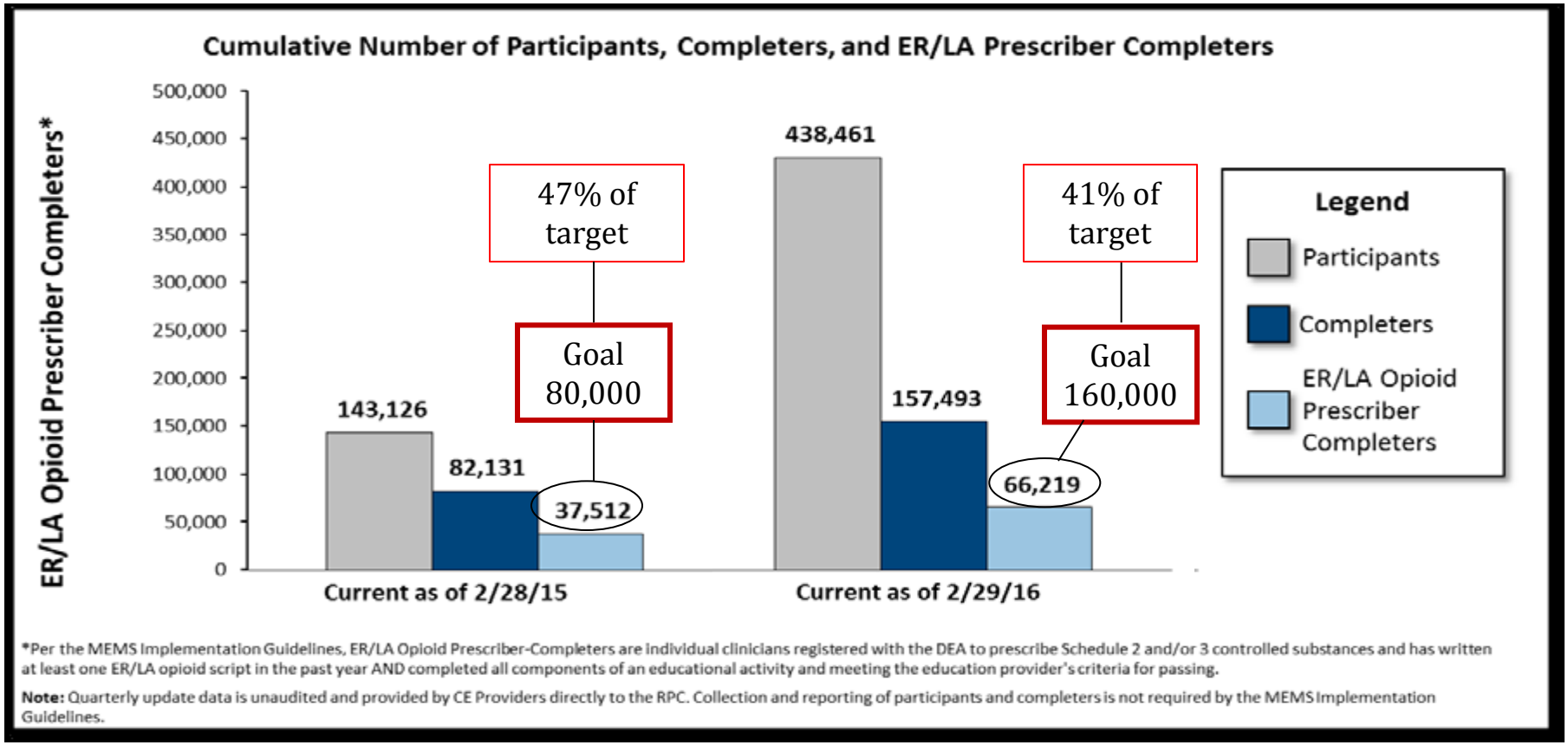
DATES	ACCREDITED REMS-COMPLIANT CE ACTIVITIES LAUNCHED
February 28, 2013-May 10, 2013	9
May 11, 2013-February 28, 2014	262
March 1, 2014-February 28, 2015	253
March 1, 2015-February 29, 2016	315
TOTAL	**839**

Types of trainings have been generally Live > Internet-Based > Print

Definitions of Terms

- **REMS-Compliant Training:**
  - offered by an accredited CE provider
  - all elements of the FDA Blueprint;
  - knowledge assessment tests for all Blueprint sections
  - subject to independent audit
- **Participant**- partial completer of a CE activity
- **Completer**- one who completed all components of a CE activity and met the criteria for passing
- **ER/LA Prescriber Completer-** Completer registered with the DEA to prescribe Schedule II and/or III controlled substances and has written at least one ER/LA prescription in the past year (self-identified)

RPC Training Numbers



*Per the MEMS Implementation Guidelines, ER/LA Opioid Prescriber-Completers are individual clinicians registered with the DEA to prescribe Schedule 2 and/or 3 controlled substances and has written at least one ER/LA opioid script in the past year AND completed all components of an educational activity and meeting the education provider's criteria for passing.

Note: Quarterly update data is unaudited and provided by CE Providers directly to the RPC. Collection and reporting of participants and completers is not required by the MEMS Implementation Guidelines.

Independent Audit Findings

- Audit of at least 10% of the RPC- funded REMS-Compliant training to evaluate whether:
  - training covers all elements of the Blueprint;
  - post-course knowledge assessment measures all sections of the Blueprint;
  - training was conducted in accordance with ACCME or appropriate accreditation standards
- **Results**: 10% of RPC-funded CE were audited and **69%** met all criteria for REMS-compliant CE.
  - Primary reason for 31% not meeting criteria: issues of disclosure financial relationships.

On to Ms. Harris and Dr. Hsueh….

Extended Release and Long-Acting Opioid Analgesics (ER/LA) REMS 36-Month Assessment: Review of Prescriber and Patient Surveys

Shelly Harris, MPH
REMS Assessment Analyst
Division of Risk Management (DRISK)
Ya-Hui Hsueh, PhD
Mathematical Statistician
Division of Biometrics VII (DB7)

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM)
and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
May 3-4, 2016

Presentation Outline

- Overview of the REMS Survey Review Process (Ms. Harris)
- Review of ER/LA REMS Knowledge, Attitude, and Behaviors (KAB) surveys (Ms. Harris)
  - Follow-up Prescriber Survey
  - Long-Term Evaluation (LTE) Prescriber Survey
  - Patient Survey
- Statistical Evaluation (Dr. Hsueh)
  - Comparability
  - Validity
  - Generalizability
  - Future Considerations
- Overall Conclusions (Ms. Harris)

REMS Assessment Process: Survey Review

- If REMS Assessment Plan includes surveys, we encourage the sponsor to submit a survey methodology protocol for FDA review.
- The methodology is reviewed by DRISK social scientists along with other FDA Divisions as needed through consultation.
- FDA provides recommendations back to the sponsor on the survey methodology for inclusion before survey implementation.
- The final review of the survey results is a part of the overall assessment of whether or not the REMS is meeting its goals.

REMS Assessment Process: Survey Design

- To date, the majority of REMS assessments have used cross-sectional surveys of prescribers and patients. Many use convenience samples as well for recruitment of participants.
- We encourage all sponsors to complete pre-testing/qualitative testing of the surveys.
- We ask sponsor to set target knowledge rates; which is the minimum knowledge rate that, if achieved, determines that the REMS met its goal of communicating the REMS key messages.
  - 80% is a generally acceptable target
- There is a FDA guidance currently in development that address some of these survey design considerations.

ER/LA Opioid Analgesics REMS Prescriber and Patient Surveys Timeline

2012

July 2012: ER/LA Opioid Analgesics REMS Approved with FDA Blueprint

December 2012: Year 1 (24-Month) Patient Survey launched

2013

February 2013: Pre-REMS Prescriber KAB Survey launched

February 28, 2013: 1st REMS Compliant training available

September 2013: Year 2 (36-Month) Patient Survey launched

2014

2015

February 2015: Follow-up Prescriber Survey and Long-Term Evaluation Prescriber Survey launched

2016

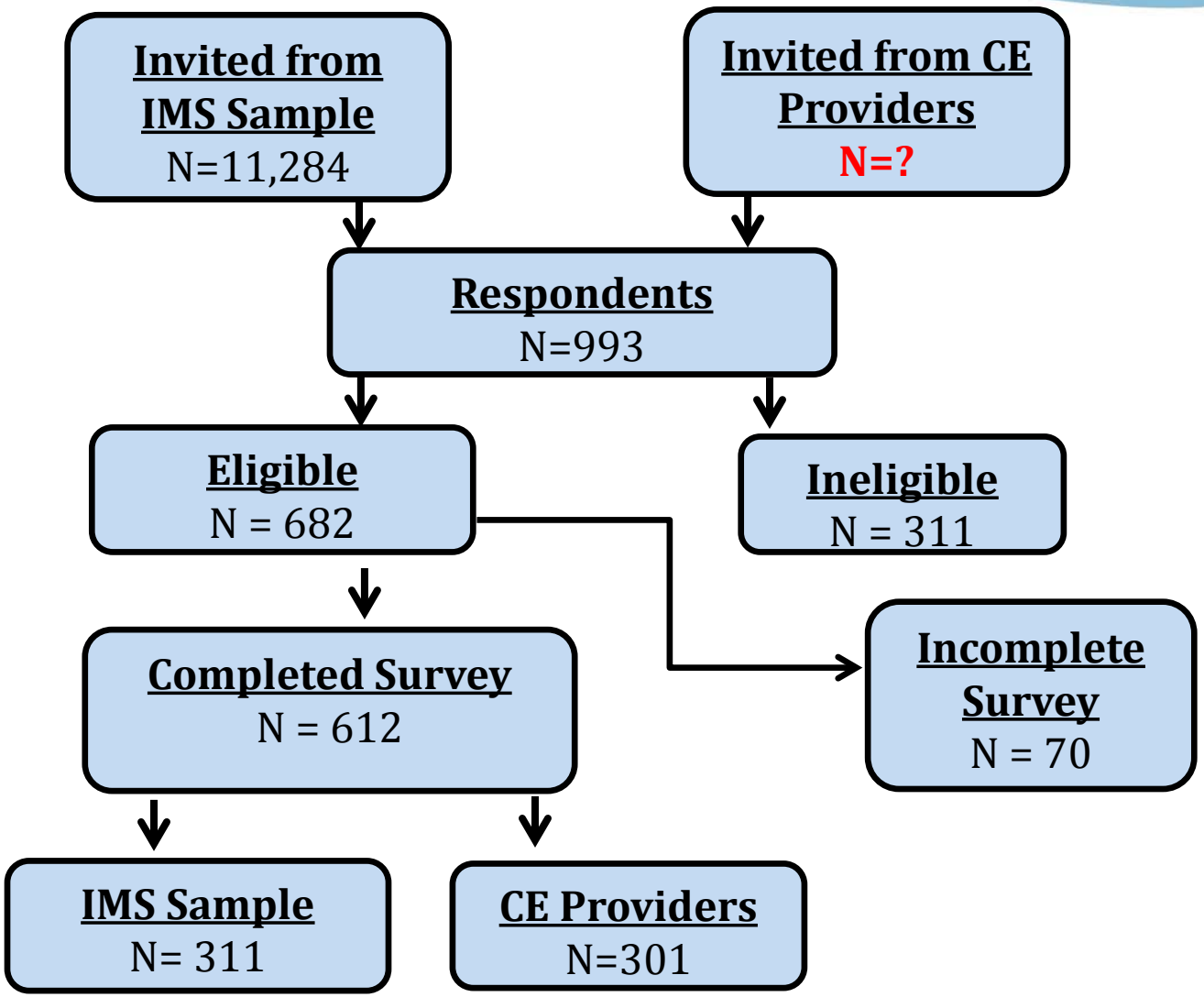
Element 3a: Follow-up Prescriber Survey

Follow-up Survey: Purpose

- To assess prescribers' awareness and understanding of the serious risks associated with the use of ER/LA opioid analgesics and appropriate prescribing of ER/LA opioid analgesics
  - To compare prescribers who:
    - completed a REMS-compliant continuing education (CE) activity (recruited from CE providers)
    - have not completed a REMS-compliant CE activity (recruited from IMS sample)
  - Pre-REMS knowledge survey was conducted to assess knowledge and prescribing behaviors before implementation of the REMS program (n=605)

Follow-Up Prescriber Survey Respondents

Eligible Respondents: Prescribers who prescribed an ER/LA opioid analgesic at least once in the previous 12 months



Follow-up Prescriber Survey: Prescriber Characteristics

Health Profession:
54%: MD/DO
25%: Nurse Practitioner/ Advanced Practice Nurse
22%: Physician Assistant

Specialty:
45%: General Practice/ Internal Medicine
22%: Pain management
33%: Other

Most commonly prescribed ER/LA opioid analgesics:
70%: Oxycodone
69%: Fentanyl
68%: Morphine

53% prescribed ER/LA opioid analgesics 10 or fewer times in the past month

34% practiced medicine for more than 10 years

Geographic Region:
32%: West
21%: Central
19%: South
18%: East
10%: Northeast

Follow-up Prescriber Survey: Key Risk Messages (KRM) and Topics

FDA Blueprint Domains

KRM 1: Assessing patients for treatment

KRM 2: Initiating, modifying, and discontinuing therapy

KRM 3: Managing ongoing therapy

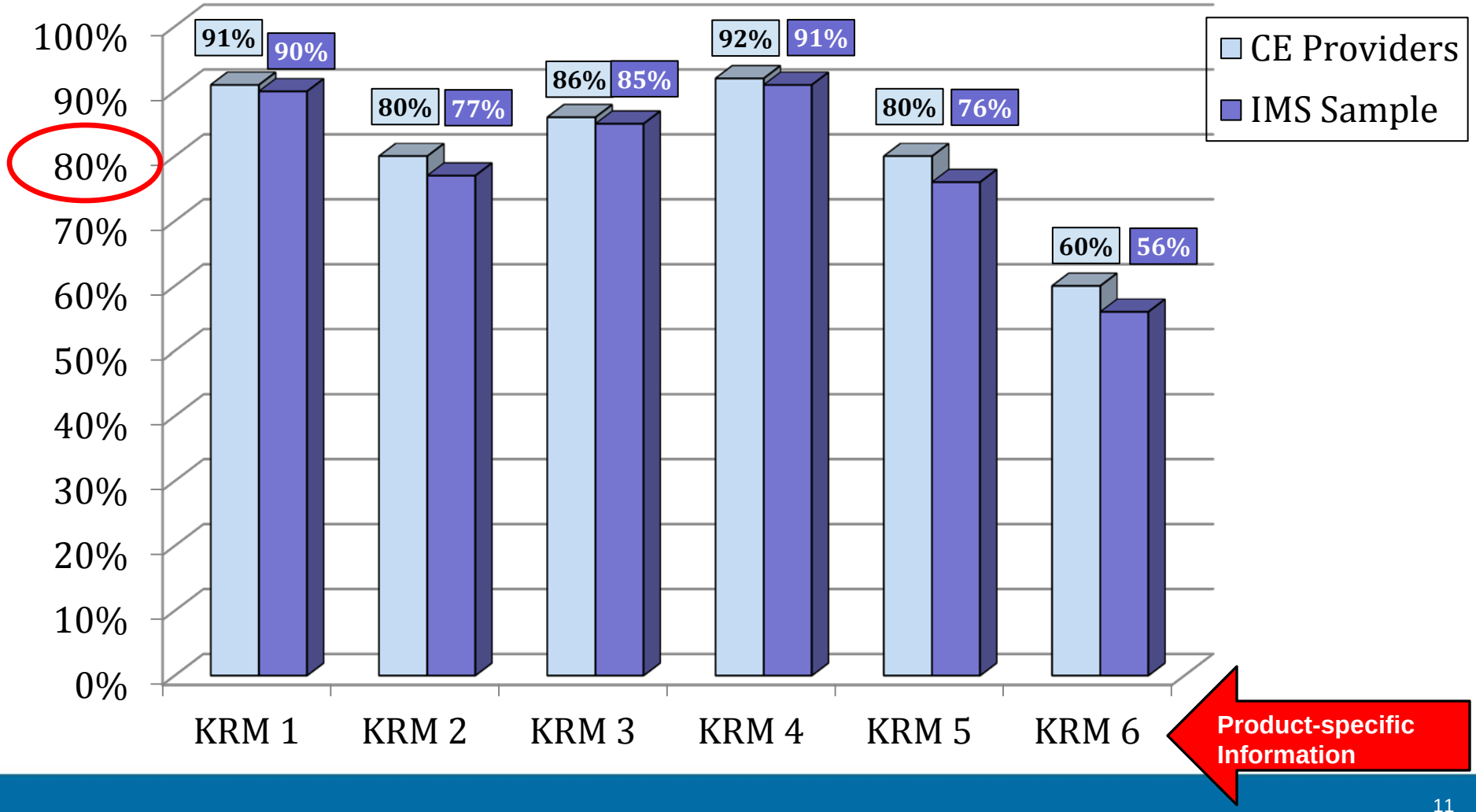
KRM 4: Counseling patients and caregivers about safe use

KRM 5: General drug information

KRM 6: Product specific information

- Awareness of REMS Materials
- Patient Access to Opioids
- Prescriber Behaviors

Follow-Up Prescriber Survey: Percent Knowledge Rates by Key Risk Message (KRM)



Follow-up Prescriber Survey: Self-Reported Prescriber Behaviors and Awareness of REMS Materials

Healthcare providers always or regularly:

- **96%:** Counsel patients about important risks
- **76%:** Complete a Patient Prescriber Agreement when first prescribing the ERLA
- **49%**: Use the Patient Counseling Document
  - **55%** CE Providers versus **44%** IMS Sample

Awareness of REMS Materials

- Overall awareness of REMS materials was low.
- Respondents from CE providers had a higher awareness of REMS materials than IMS sample respondents.

Follow-up Prescriber Survey: Prescriber's Perceptions of Patient Access

Impact of the REMS on patient access:

- **38%:** Thought the REMS added difficulty to patient access
- **37%:** Reported no impact
- **22%:** Did not know
- **3%:** Made it easier for patient access

Main obstacles to patient access to opioids:

- **74%**: Insurance coverage
- **72%**: Insurance authorizations and approvals
- **55%**: Patient's ability to pay

Follow-up Survey: Self-Reported Changes in Prescribing Behaviors

Since the implementation of the REMS:

- **48%**: No change in prescribing
- **23%**: Limiting which ER/LAs they prescribe
- **23%**: Prescribe more non-opioid medications
  - ***27%*** *of CE providers vs.* ***18%*** *of IMS sample*
- **18%:** Prescribe fewer ER/LAs
- **11%:** Prescribe more ER/LAs
- **9%:** Prescribe more IR opioid medications
  - ***11%*** *of CE providers vs.* ***6%*** *of IMS sample*

Follow-up Prescriber Survey Comments

Across all key risk messages, completing a REMS-compliant CE activity increased the likelihood of answering questions correctly

- High volume prescribers (prescribing ER/LAs 11 or more times per month) were more likely to answer questions correctly across most key risk messages.
- Overall knowledge rates and prescriber behaviors recommended in the Blueprint improved from the Pre-REMS survey to the follow-up survey.

Sample concerns

- 54% of prescribers recruited from the IMS sample self-reported completing a REMS- compliant CE activity.
- Limited data on respondents recruited from CE Providers

Prescriber Awareness of the REMS

- Prescribers had a low awareness of REMS materials.
- With various training efforts occurring (state, local, federal), not sure if prescribers are aware of which CE trainings/activities are considered REMS-compliant.
- 12% of CE completers indicated that they did not complete a REMS-compliant CE activity.

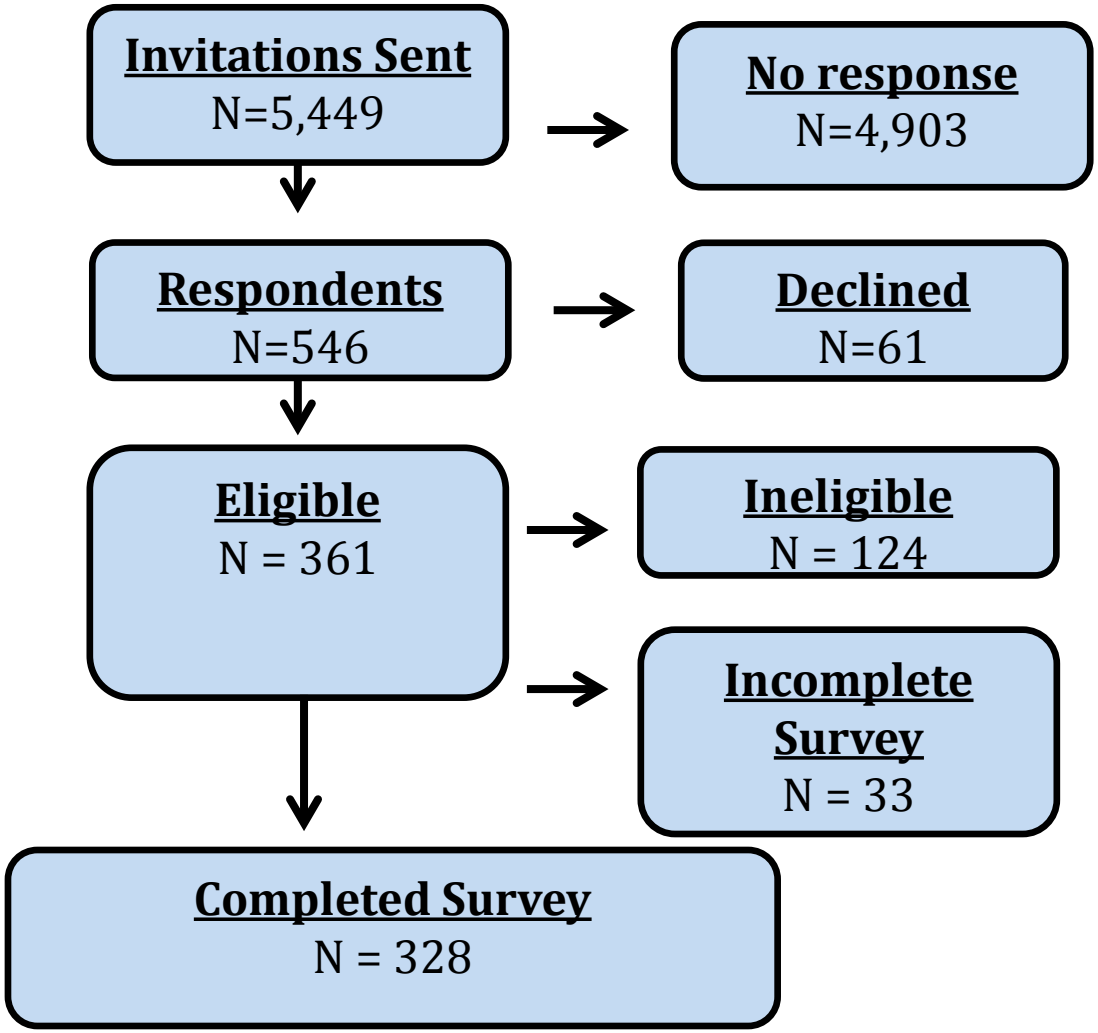
Element 3b: Long-Term Evaluation (LTE) Prescriber Survey

LTE Prescriber Survey

- **Purpose**: To assess prescribers' knowledge retention and practice changes 6 months to one year after completion of a REMS compliant CE
  - Includes a subset of questions from the Follow-up prescriber survey along with case-based scenarios

LTE Prescriber Survey Respondents

- **Eligible Respondents:** Prescribers who completed an ER/LA opioid analgesic REMS-compliant activity in the previous 6 to 12 months



LTE Survey: Prescriber Characteristics

Health Profession:
66%: MD/DO
26%: Nurse Practitioner/Advanced Practice Nurse
8%: Physician Assistant

Specialty:
28%: Pain management
22% General/Family Practice
Internal Medicine
12%: Hospice/Palliative care
38%: Other

Most commonly prescribed ER/LA opioid analgesics:
71%: Oxycodone
68%: Morphine
67%: Fentanyl

52% prescribed ER/LA opioid analgesics 10 or fewer times in the past month

60% practiced medicine for more than 15 years

Geographic Region:
40%: West
22%: Central
15%: South
14%: Northeast
9%: East

LTE Prescriber Survey: Key Risk Messages (KRM) and Topics

FDA Blueprint Domains

KRM 1: Assessing patients for treatment

KRM 2: Initiating, modifying, and discontinuing therapy

KRM 3: Managing ongoing therapy

KRM 4: Counseling patients and caregivers about safe use

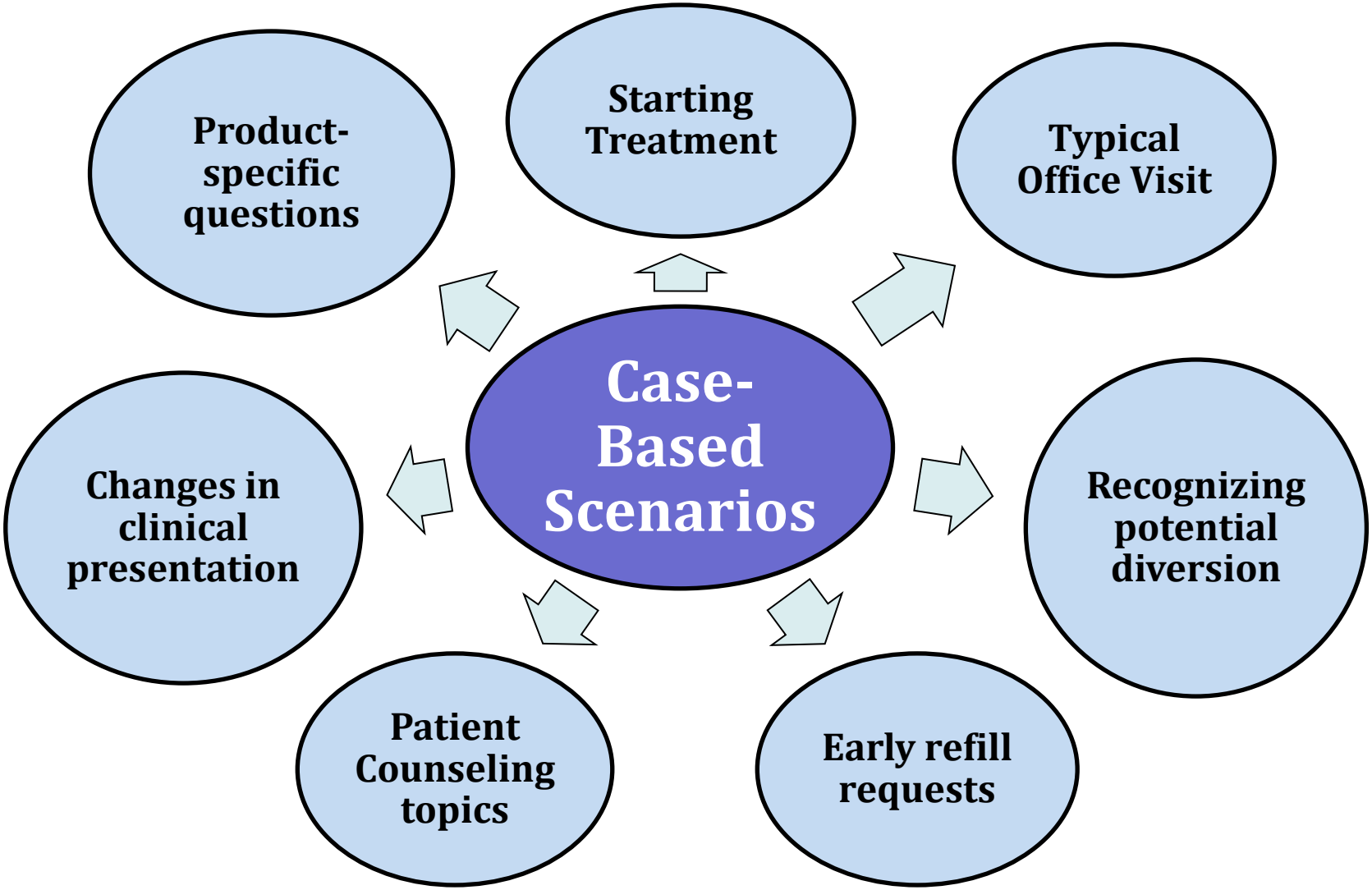
KRM 5: General drug information

KRM 6: Product specific information

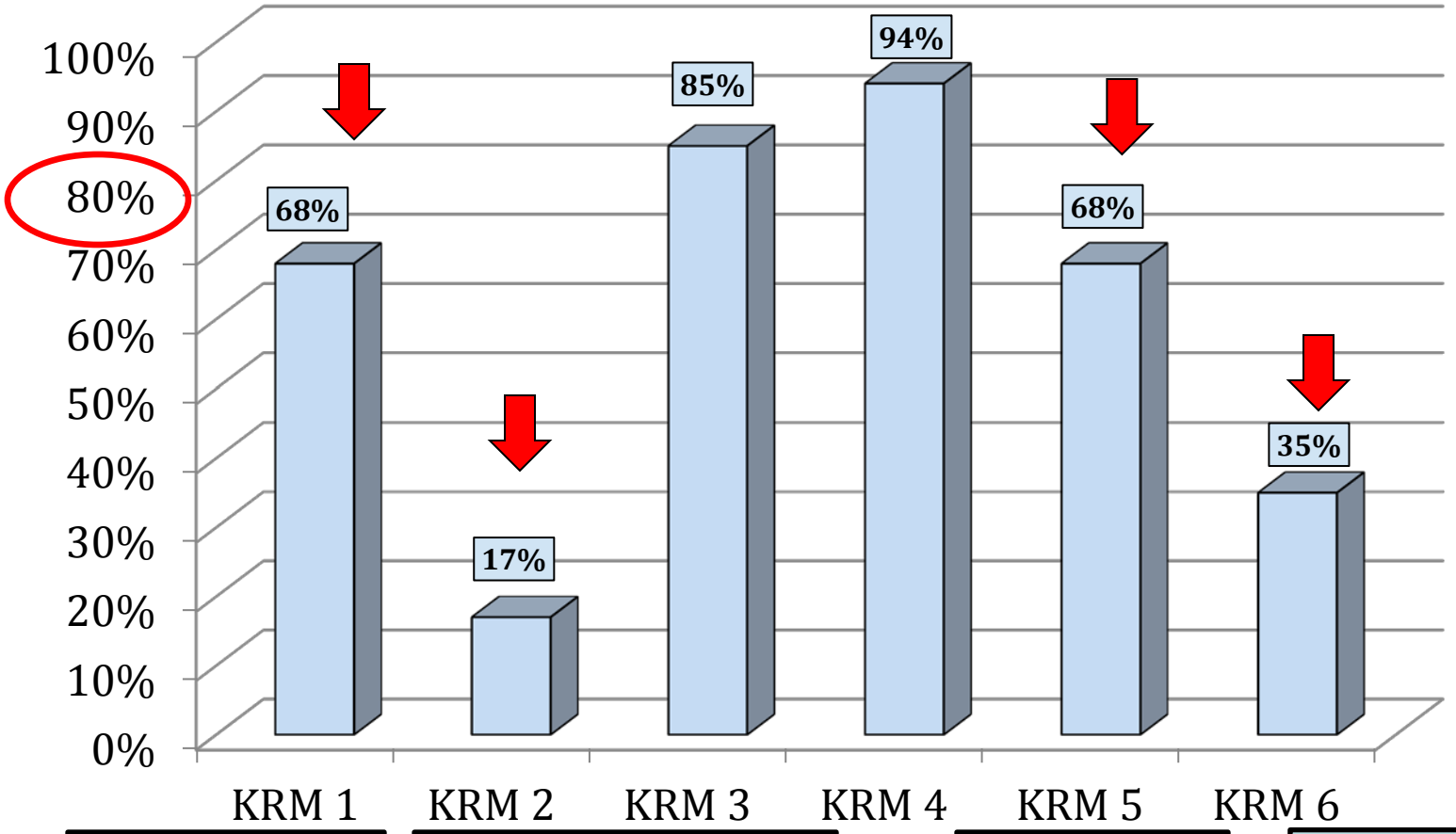
- Awareness of REMS Materials
- Patient Access to Opioids
- Prescriber Behaviors

Case-Based Scenarios Across Domains

Case-Based Scenarios



LTE Prescriber Survey: Percent Knowledge Rates by Key Risk Message (KRM)



KRM 1	KRM 2	KRM 3	KRM 4	KRM 5	KRM 6
Assessing patients for treatment	Initiating, modifying, and discontinuing therapy		General drug info		Product-specific info.

LTE Survey: Prescriber Self-Reported Behaviors

Since completing a REMS-compliant CE activity:

- **32%:** No change in prescribing
- **38%:** Prescribe more non-opioids
- **23%:** Limiting which ER/LAs prescribed
- **18%:** Prescribe more ER/LAs
- **13%:** Prescribe fewer ER/LAs
- **8%:** Prescribe more IR opioids

Respondents more often:

- **64%:** Checked the state prescription monitoring program (PMP)
- **48%:** Completed a Patient Prescriber Agreement (PPA)
- **39%:** Used the Patient Counseling Document (PCD) for discussions with patients

LTE Prescriber Survey: Barriers to Change

Barriers to applying information learned in REMS-complaint CE trainings:

- **64%**: Insufficient time during clinical encounters
- **57%**: Patient non-compliance
- **48%**: Patients continuing to identify new ways of drug seeking behavior not addressed in the training

LTE Prescriber Survey Comments

Knowledge rates did not reach the target for 4 out of the 6 key risk messages.

- A greater number of lower scoring items were case-based scenario questions suggesting respondents may understand the information but are not able to apply the information to a real patient scenario.
- For product -specific scenarios, prescribers may not have prescribed that particular ER/LA opioid analgesic .

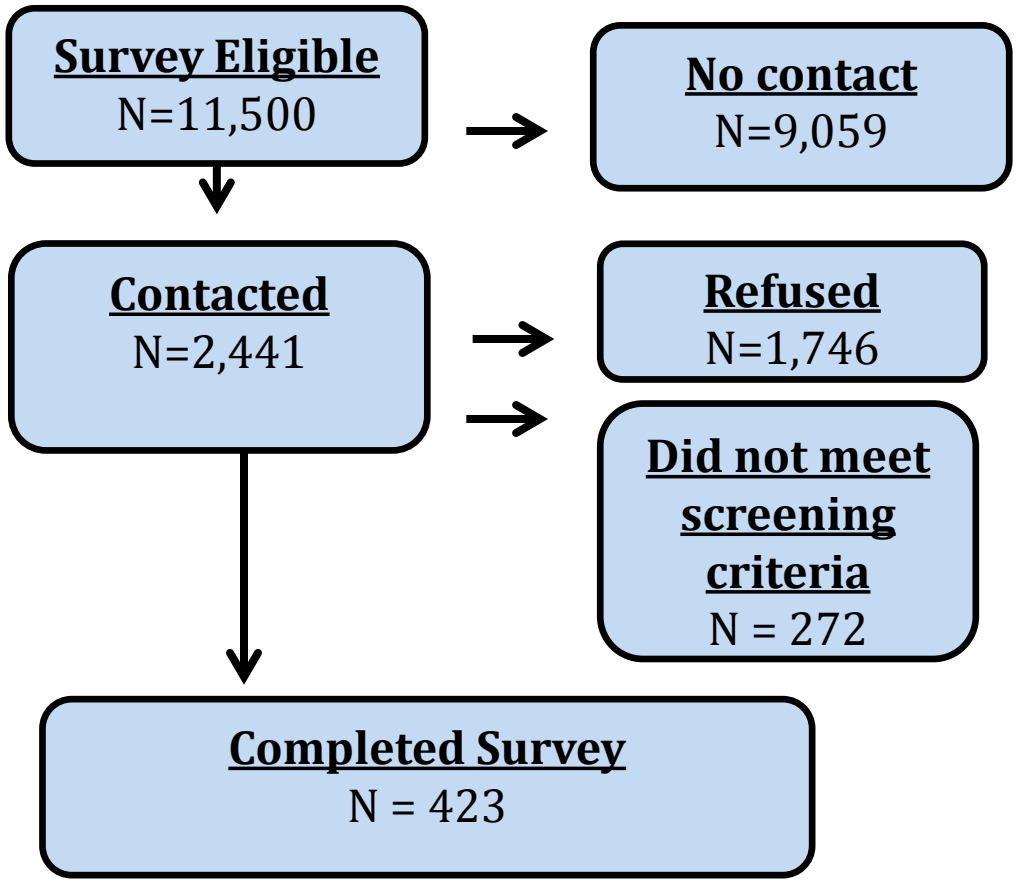
Sample concerns

- Limited data of respondents from CE providers
- Target sample size was not reached. Proposed sample was 600 (n=328).

Element 4: Patient Survey

Patient Survey Respondents

- **Eligible Respondents:**
  - Ages 18 or older who received at least one prescription for an ER/LA opioid analgesic within the past 12 months
  - Identified from the HealthCore Integrated Research Database (HIRD)
  - Limited to commercially insured patients



Patient Survey: Patient Characteristics

Race:
94%: Caucasian
3%: African-American
1%: Mixed-race background

Annual Income:
12%: Less than $25,000
26%: $25,000 to $49,000
22%: $50,000 to $74,999
13%: $75,000 to $99,000
21%: $100,000 or more

Age:
0%: <18
12%: 18-24
27%: 35-49
56%: 50-64
5%: 65+

Education Level:
<1%: Some high school
19%: High school graduate/GED
38%: Some college/Two-year degree
26%: College Graduate
11%: Completed Graduate School

Geographic Region:
33%: Midwest
32%: West
26%: South
13%: Northeast

83% had used an ER/LA before
16% were new users

Gender:
60%: Female
40%: Male

Patient Survey Key Risk Messages (KRM) and Domains

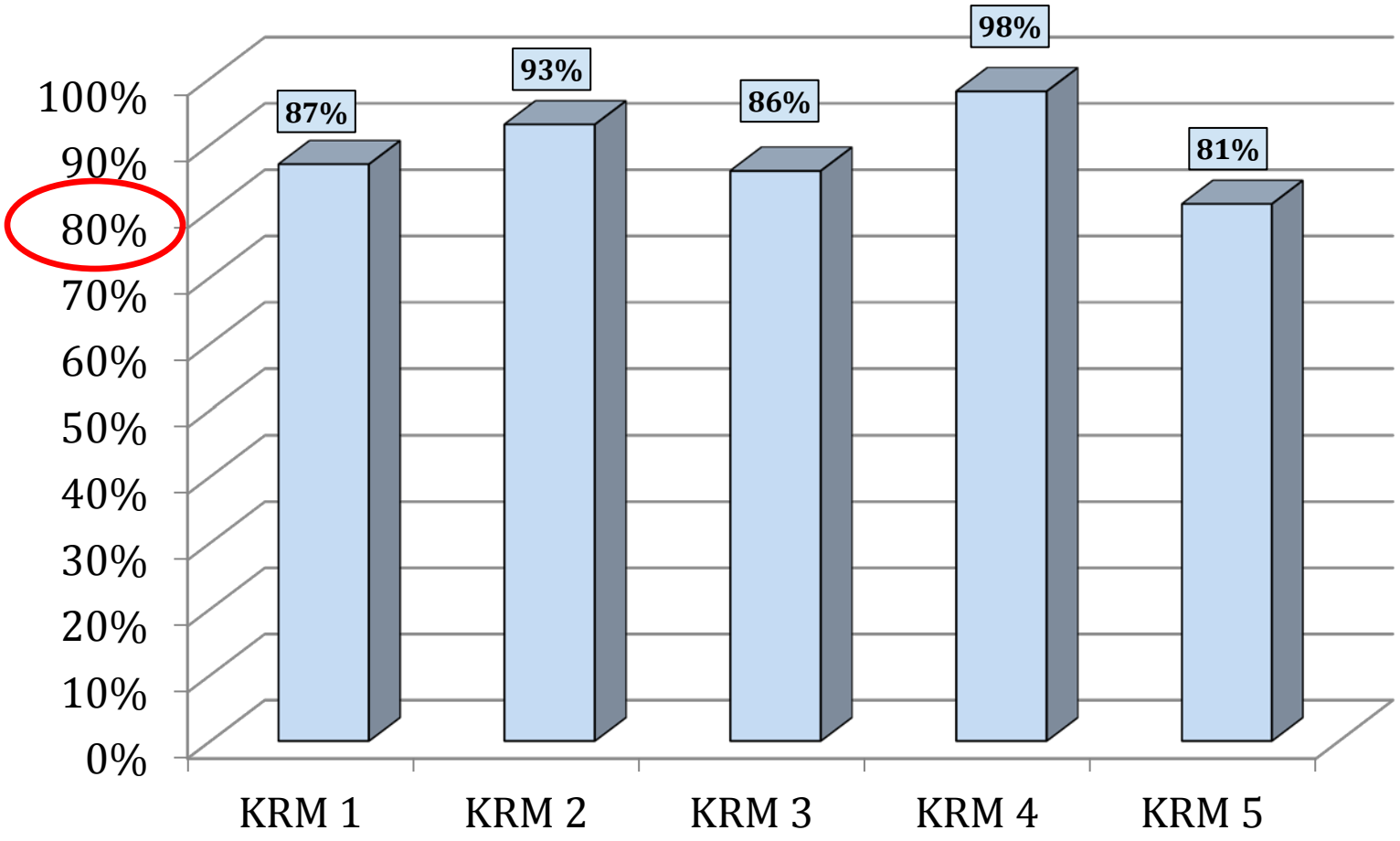
Domain 1:
Patient understanding of the serious risks of ER/LA opioid analgesics

KRM 1:	KRM 2:	KRM 3:	KRM 4:	KRM 5:
Understanding of serious risks	What to do if you take too much drug	Need to store the drug in a safe place	Not to share the drug	How to use the drug safely

Additional Domains:

- Receipt and comprehension of the Medication Guide (MG) and patient counseling document (PCD)
- Access and satisfaction with access to pain medications
- Patient -reported prescriber behaviors

Patient Survey: Percent Knowledge Rates by Key Risk Message (KRM)



Patient Survey: Patient-Reported Prescriber Behaviors and Receipt of REMS Materials

Healthcare provider always or regularly:

- **54%**: Cautioned about the risks associated with ER/LA opioid analgesics
- **50%**: Cautioned on side effects
- **26%**: Used the patient counseling document (PCD) for discussion

Receipt of REMS Materials

- **94%:** Received the Medication Guide with their last fill
- **38%:** Received the Patient Counseling Document when first prescribed an ER/LA opioid

Patient Survey: Patient's Perceptions of Access

Perceptions of access to ER/LA opioid analgesics:

- **83%:** Satisfaction with their ability to get an opioid prescription if needed
- **78%:** Satisfaction with access to treatment with ER/LA opioid analgesics
- **46%**: Need to see HCP too often when a prescription is needed

Patient Survey Comments

Knowledge was high (≥ 80%) across the key risk messages.

- Lower awareness of safe storage of ER/LA opioid analgesics and the need to read the medication guide with each prescription
- Most patients reported satisfaction with their access to opioids and thought they could obtain an ERLA if needed for pain.

Sample concerns

- All survey respondents were commercially insured.
- Most respondents were Caucasian, with some college or higher, and over half had incomes of $50,000 or more per year.
- No patient caregivers were included as survey respondents.

Presentation Outline

- Overview of the REMS Survey Review Process (DRISK)
- Review of ER/LA REMS Knowledge, Attitude, and Behaviors (KAB) surveys (Ms. Harris)
  - Follow-up Prescriber Survey
  - Long-Term Evaluation (LTE) Prescriber Survey
  - Patient Survey
- Statistical Evaluation (Dr. Hsueh)
  - Comparability
  - Validity
  - Generalizability
  - Future Considerations
- Overall Conclusions (Ms. Harris)

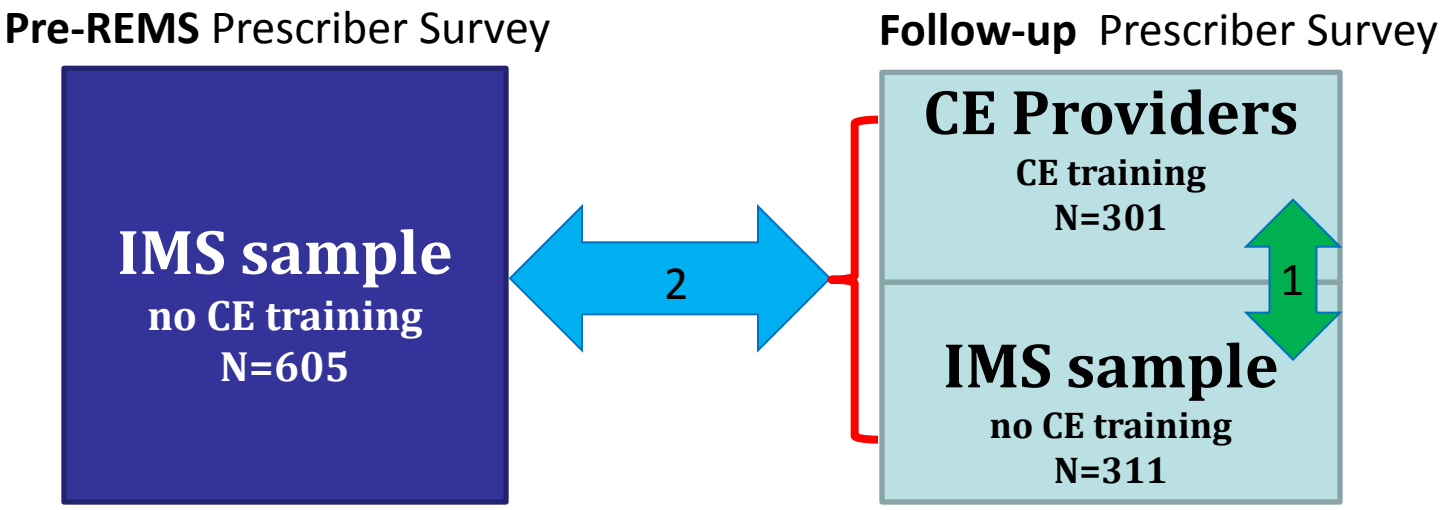
Statistical Evaluation of REMS Assessment Surveys

	Comparability	Validity	Generalizability
Element 3a: **Follow-up Prescriber Survey** IMS sample, CE provider sample, Pre-REMS sample	X	X	X
Element 3b: **Long-Term Evaluation (LTE) Prescriber Survey**		X	X
Element 4: **Patient Survey**			X

Comparability

Are populations similar?

Comparability



RPC compared Prescriber knowledge rates:

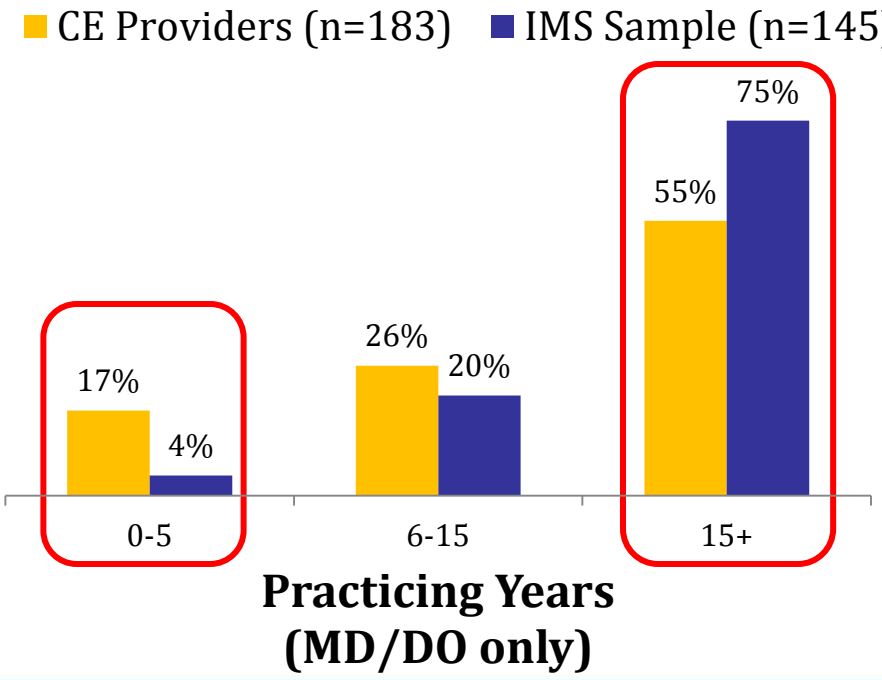
(1) CE Providers vs. IMS Sample

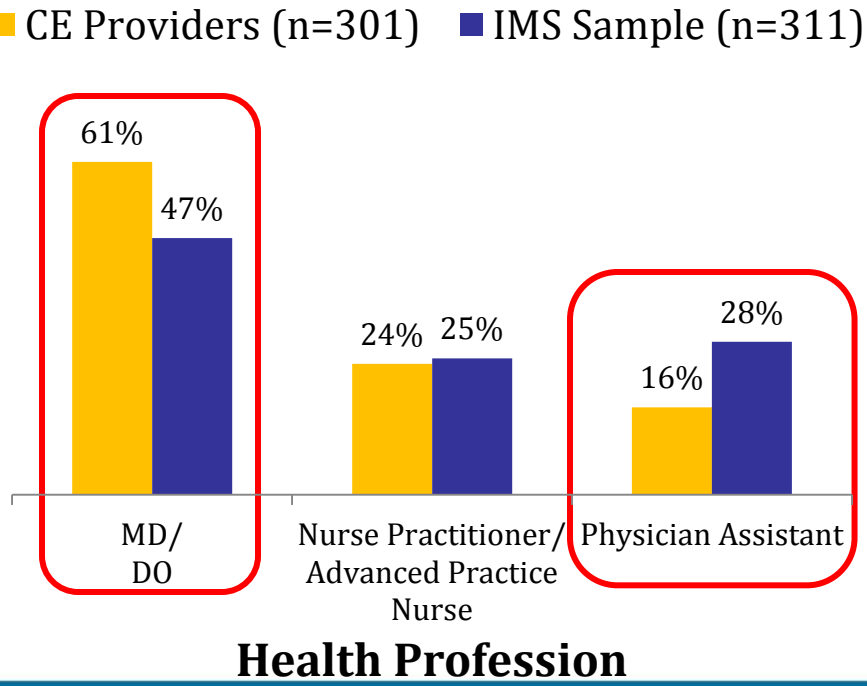
(2) Pre-REMS vs. Follow-up surveys

CE Providers vs. IMS Sample

Comparison of Prescriber Characteristics

- The two samples **are not comparable:** health profession, primary medical specialty, geographical region, past month prescription volume, practicing years
- Some of these characteristics could impact knowledge

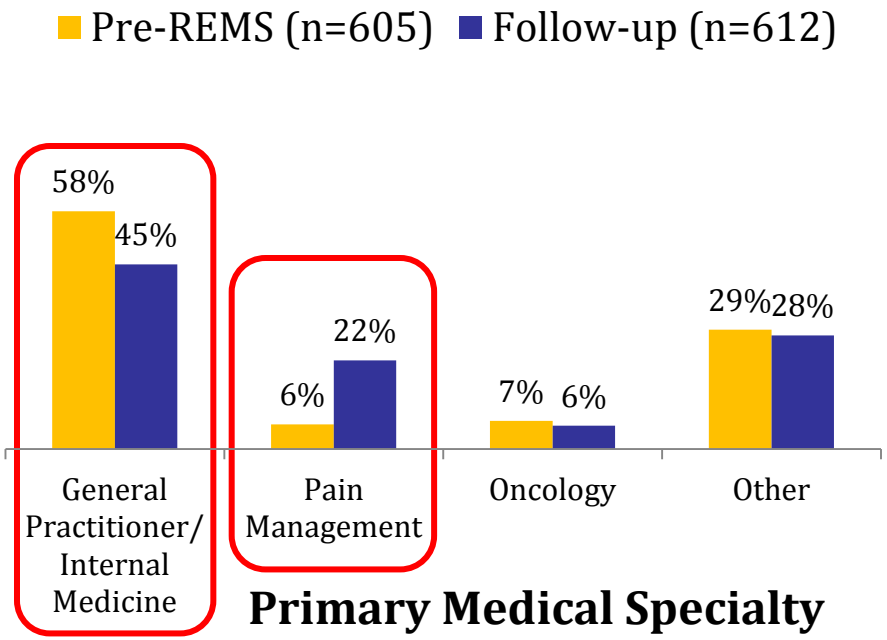




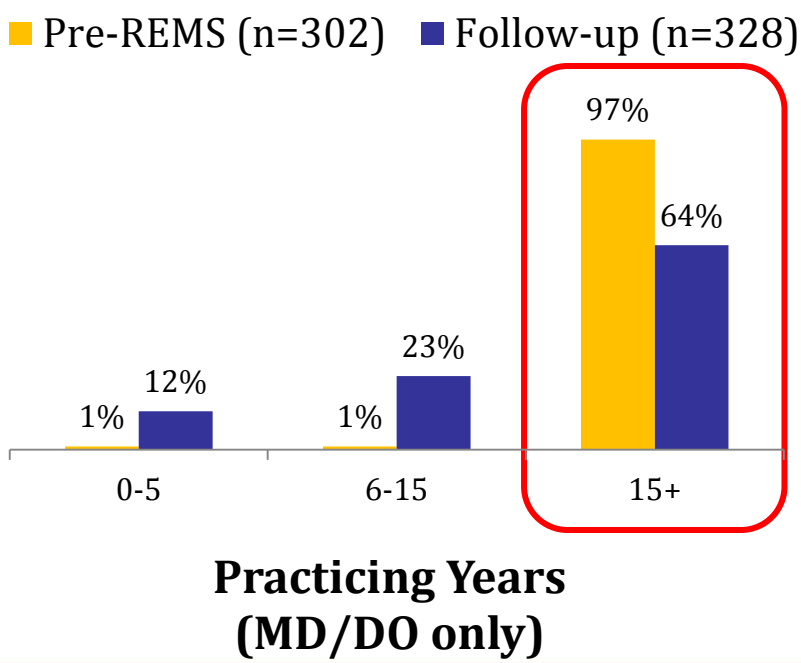
Pre-REMS vs. Follow-up Survey

Comparison of Prescriber Characteristics

- The two prescriber survey samples **are not comparable:** gender, primary medical specialty, geographical region, past month prescription volume, practicing years
- Some of these characteristics could impact knowledge



Primary Medical Specialty



Practicing Years (MD/DO only)

Validity

Are self-reported behavior accurate?

Validity

Self-reported behaviors in survey are not validated. For example,

- Number of prescriptions
- Frequency of performing urine drug screen test

Generalizability

Are survey results generalizable to the target population?

Generalizability

- Comparability
- Non-random sample
- Non response

Are Survey Samples Representative of the Target Population?

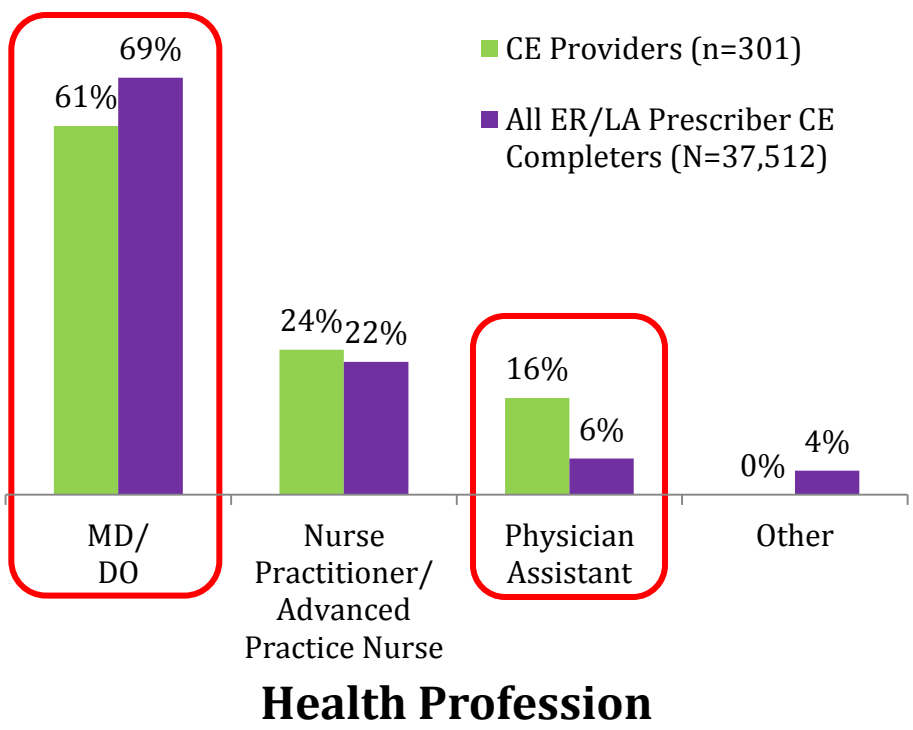
	Survey Samples	Target Population
1	CE Providers (follow-up Survey)	All ER/LA Prescriber CE Completers*
2	IMS Sample (follow-up Survey)	All ER/LA Prescribers**
3	Long-Term Evaluation (LTE) Survey	All ER/LA Prescriber CE Completers*
4	Patient Survey	Drug Use Data***

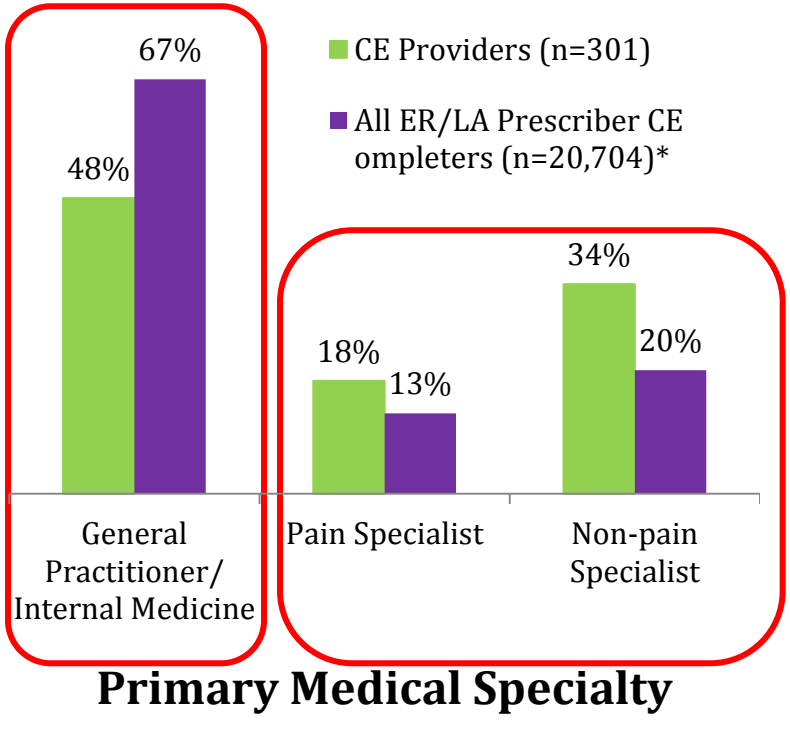
*RPC supported, accredited REMS-compliant CE completer (Feb 28, 2013-Feb 28, 2015)
**IMS database extracted in December 2014
***IMS projection from July 2013 to December 2014

CE Providers vs. All ER/LA Prescriber CE Completers

Comparison of Prescriber Characteristics

The survey sample **is different** from the target population: health profession and primary medical specialty



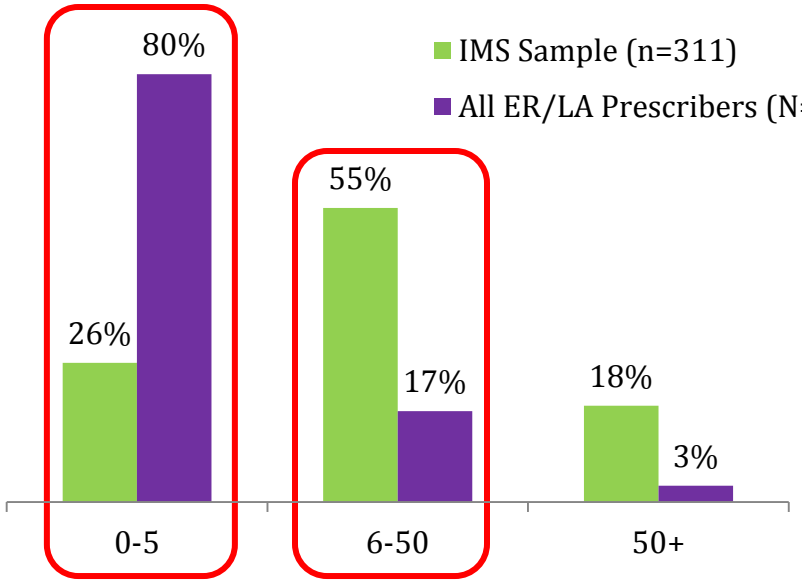


* This characteristic was captured by some CE Providers

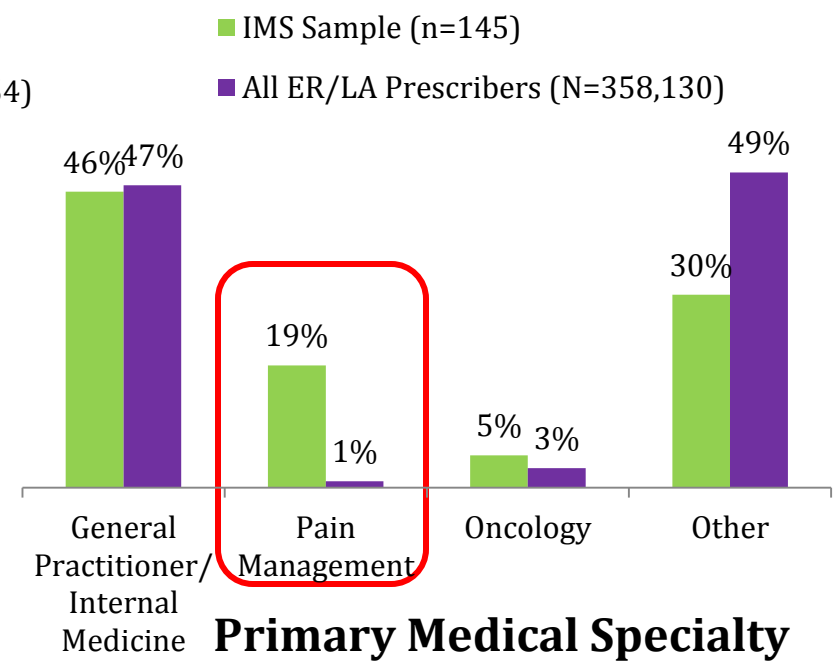
IMS Sample vs. All ER/LA Prescribers

Comparison of Prescriber Characteristics

The survey sample **is different** from the target population: past month prescription volume, primary medical specialty, health profession, region



Prescription Volume (Past Month)

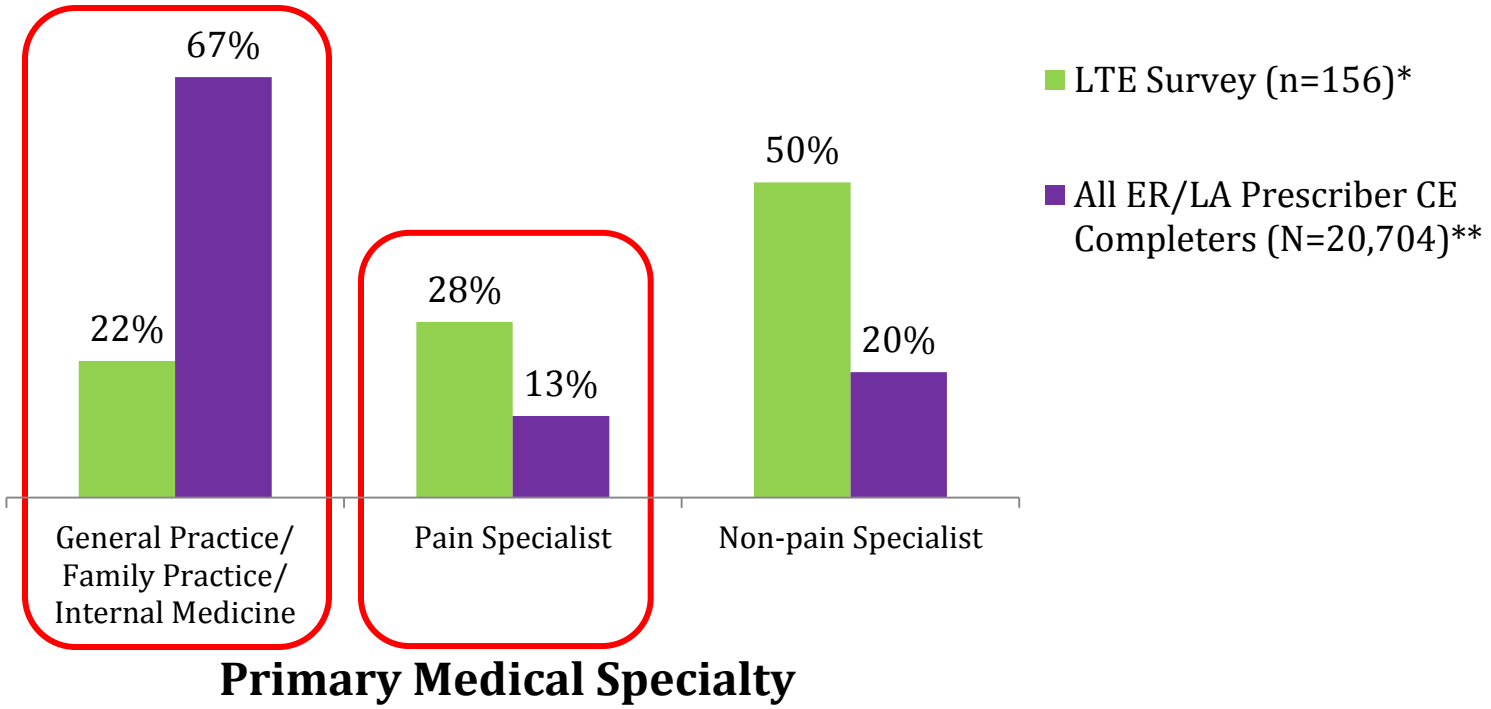


Primary Medical Specialty (MD/DO only)

LTE Survey vs. All ER/LA Prescriber CE Completers

Comparison of Prescriber Characteristics

The survey sample **is different** from the target population: primary medical specialty, health profession



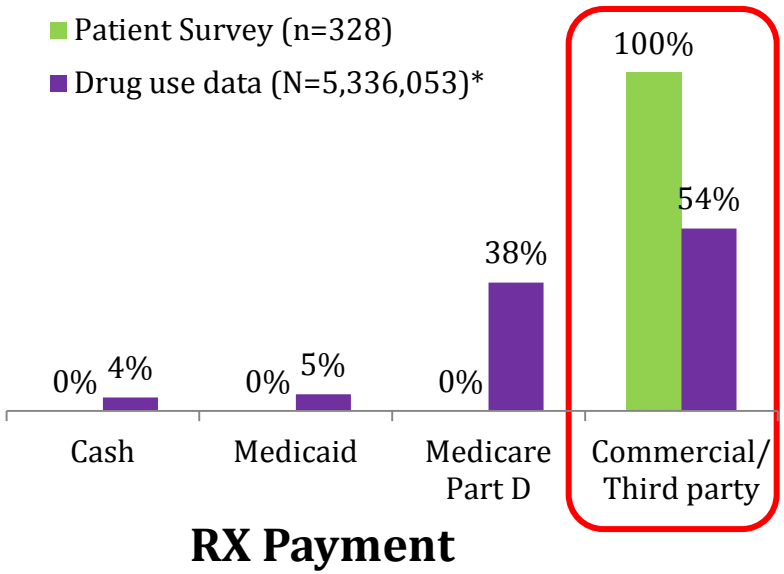
*Percentages are calculated based on the sample presented with this question because of skip logic in the survey
**This characteristic was captured by some CE Providers

Patient Survey vs. Drug Use Data

Comparison of Patient Characteristics

The survey sample

- **is not representative** of the target population: age, Rx payment, prescriber specialty
- may not be representative for race, income and education



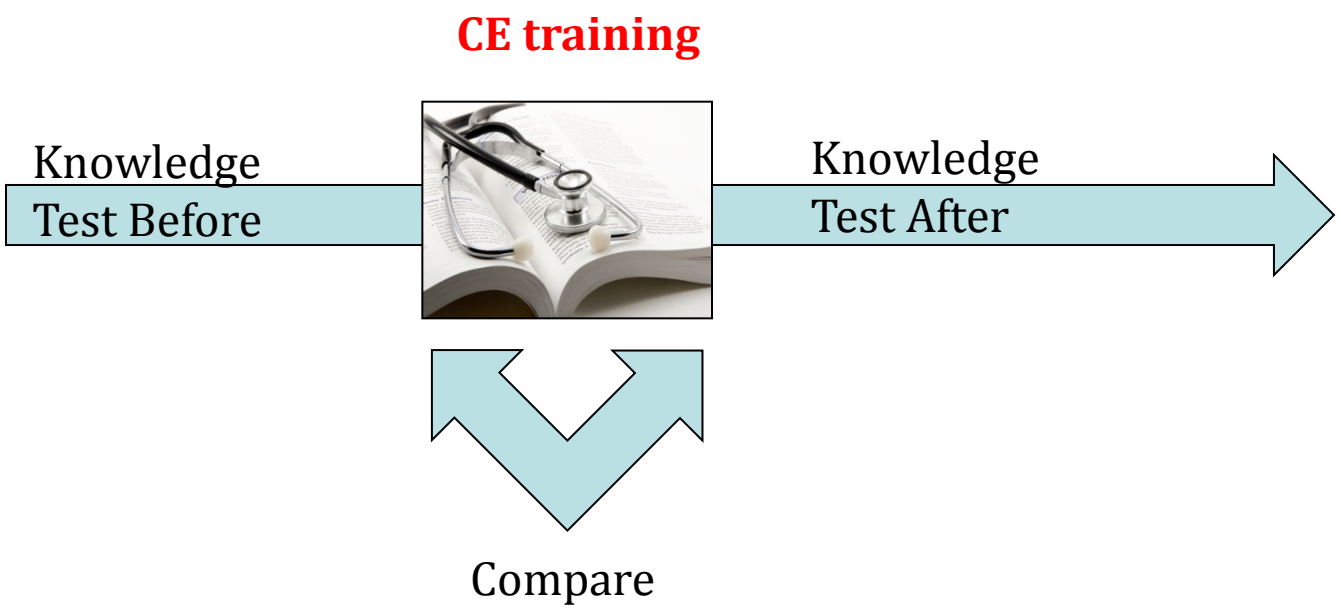
	Patient Survey (%)	Drug Use Data* (%)
Race Caucasian	94	**n/a**
Annual income at least 50,000	56	**n/a**
At least some college education	75	**n/a**

*IMS projection from July 2013 to December 2014

Considerations for Future Survey Designs

Assess the Impact of REMS CE

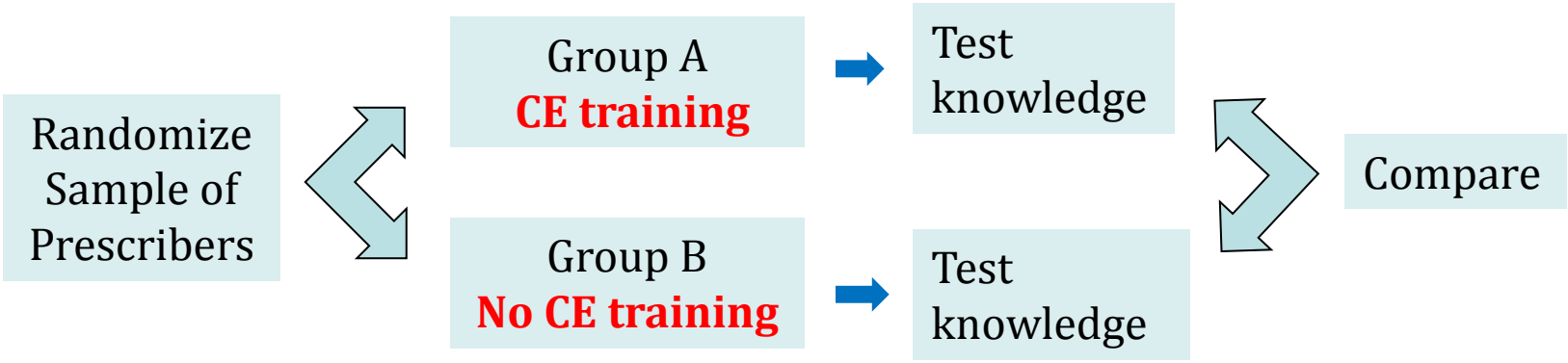
- Self-control survey on probability samples



Assess the Impact of REMS CE

continued

- Randomized experiment



Validate Self-Reported Behavior with Other Data Sources

Longitudinal database link to training data from before to after REMS CE training

- Electronic medical records
- Claims data

Generalize Survey Results to Target Population

Probability random samples

- measurable characteristics
- unmeasured characteristics

Statistical Evaluation Summary

- Survey results may have limitations of comparability, validity, and generalizability
- Prior FDA recommendations to RPC
  - Survey design and results should account for differences in baseline characteristics
  - Some survey results could be standardized to be more representative to target population
  - Additional data source for patient survey (e.g., Medicare, Medicaid)
- Considerations for future survey designs
  - probability random samples, self-control, randomized experiment, linkage to longitudinal database of behavior

Overall 36-Month Survey Review Conclusions

- In general, high knowledge rates for most of the six areas of the FDA Blueprint for both prescribers and patients.
  - Lower scoring items were most often in the domain of product-specific information and case-based scenario questions.
- Prescribers self-reported that they always or regularly conducted appropriate prescribing behaviors although patients reported a lower frequency of these same appropriate behaviors by their prescribers.
- While some prescribers reported changes in behaviors since the REMS, we are not sure why these changes occurred.

Overall 36-Month Survey Review Conclusions (2)

- Surveys have limitations.
  - Cross-sectional look at different prescribers and patients
  - Concerns about representativeness of the survey respondents
    - We have asked the RPC to provide more data on how survey respondents compare to the overall populations ER/LA prescribers, patients, and CE completers
  - The patient survey may over-estimate the effect of the REMS patient materials.
  - For the Year 3 Patient Survey, FDA recommended:
    - The use of different databases to recruit more representative populations (Medicare/Medicaid)
    - The inclusion of patient caregivers
  - Alternative survey designs should be considered.

End of Presentation

Extended-Release and Long-Acting (ER/LA) Opioid Analgesic REMS 36-month Assessment: Review of Epidemiologic and Drug Utilization Surveillance Studies

Jana McAninch, MD, MPH, MS
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Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

May 3-4, 2016

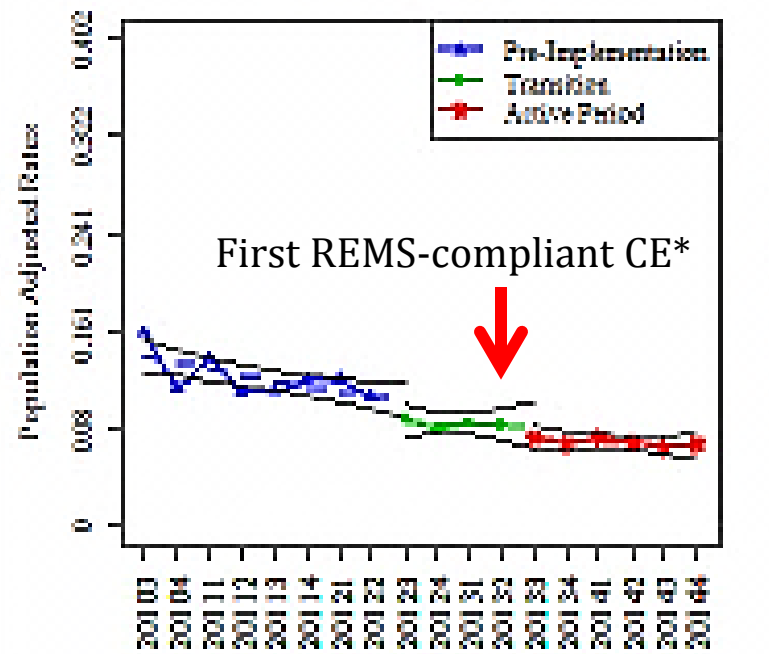
Overview

- Interpretation of the surveillance data
  - Epidemiologic studies
    - Misuse, abuse, addiction, overdose, death
  - Drug utilization data
    - Prescription volume
    - Prescribing behavior
    - Patient access
- Is the REMS making progress towards it goal?
- Considerations for future REMS assessments

Interpretation of the Epidemiologic Surveillance Studies

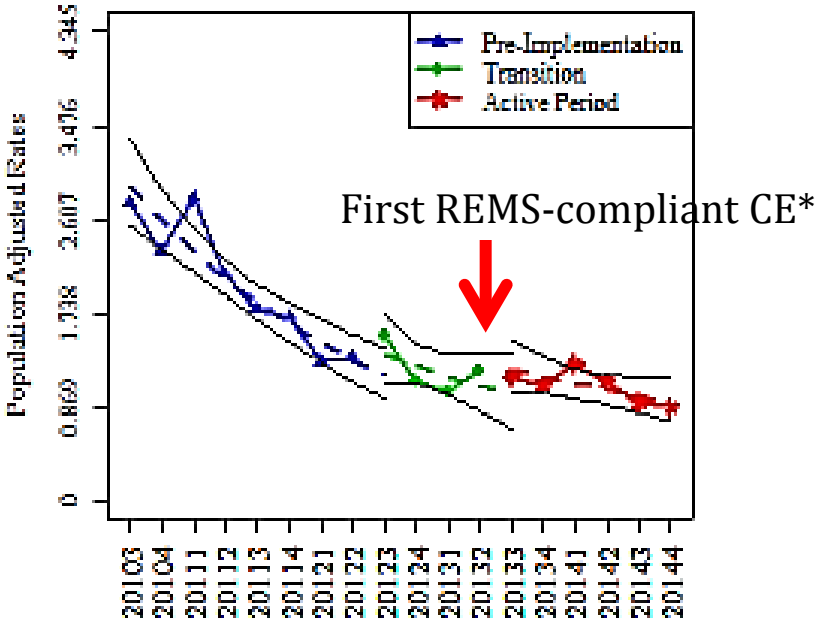
Decreases In Outcomes Began Before REMS Implemented

Example 1: ER/LA opioid related poison center exposure calls



Intentional Abuse Exposure Call Population-adjusted Rates for ER/LA Opioids, RADARS® Poison Center Program Study

Example 2: Recent ER/LA opioid abuse in people entering opioid addiction treatment

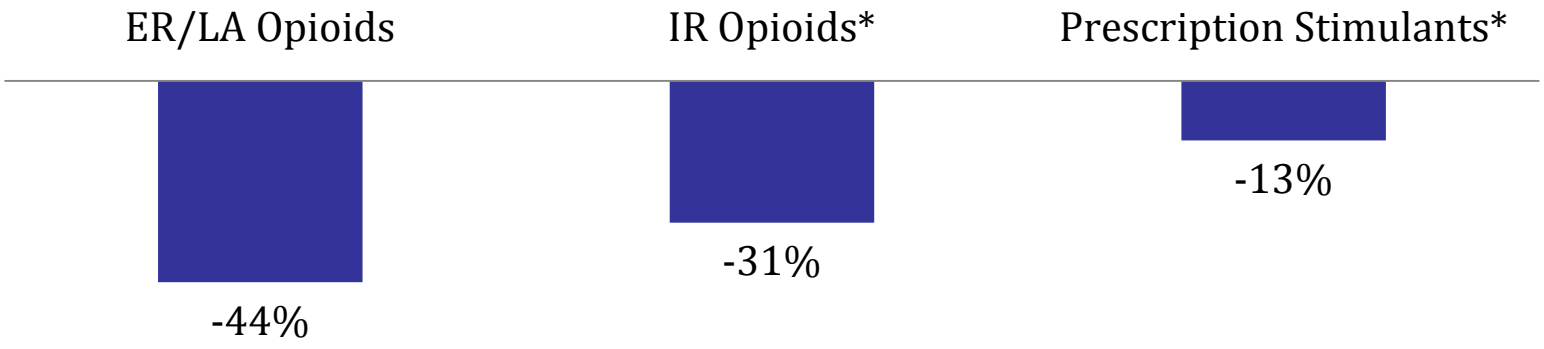


Self-reported Past Month Abuse Population-adjusted Rates for ER/LA Opioids, RADARS® Treatment Center Program study

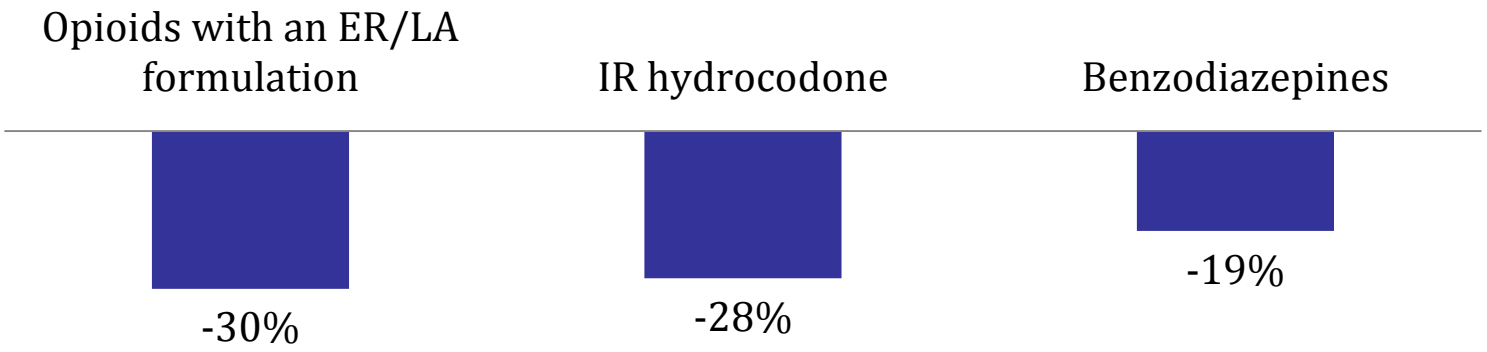
*CE=Continuing Education

Observed Decreases Not Limited To ER/LA Opioids

<u>Example 1:</u> Relative percent change in intentional abuse call rates, Pre- vs. Active REMS study period (RADARS® Poison Center Program study)



<u>Example 2:</u> Relative percent change in overdose death rates in state of Washington, Pre- vs. Active REMS study period (WA State Medical Examiner Study)

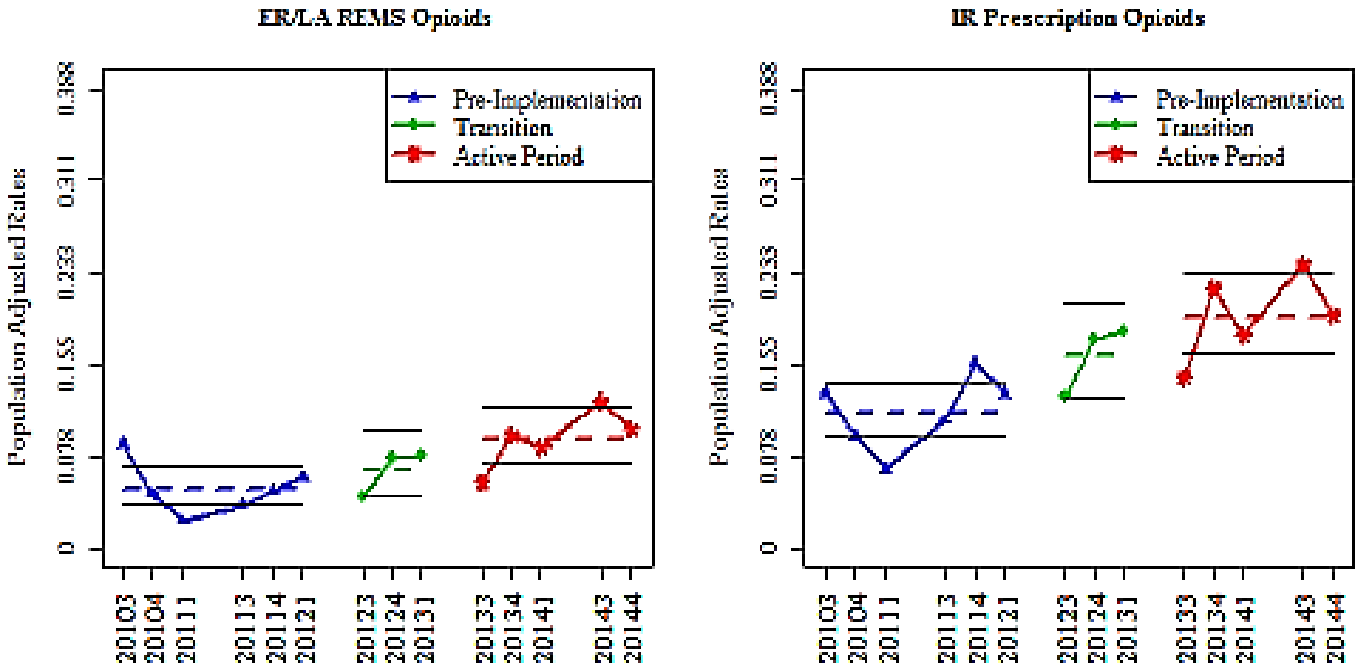


* % change significantly different from ER/LA opioids

Findings Differed Across Studies Examining Similar Outcomes

- **Example: Increases** in nonmedical ER/LA and IR opioid use in survey of college students conflict with **decreases** seen in poison center calls, treatment center abuse rates

Mean past 90-day non-medical use rates per 100,000 population for ER/LA (left panel) and IR (right panel) opioids, RADARS® College Survey study



Potential Sampling Bias

Examples:

- **Treatment Center Studies (RADARS®, NAVIPPRO®)**
  - Changes over time in
    - Site participation in surveillance network
    - Client mix
    - Treatment program capacity/access relative to need
- **RADARS® Poison Center Program study**
  - Some evidence that call data predict emergency department visit trends[1]
  - But…use of poison call centers changing:[2] may change fraction of events captured over time

1. Davis et al., *Pharmacoepidemiology and Drug Safety* 2014
2. Mowry et al., American Association of Poison Control Centers 2014 Annual Report

Data Quality Limitations: Outcome Definition, Ascertainment, and Validation

Examples:

- **HIRD[1] and Medicaid claims-based studies**
  - ICD-9 opioid overdose codes not adequately validated
  - Most fatal overdoses not captured
- **Washington State Medical Examiner study**
  - For many deaths, cannot distinguish ER/LA from IR
- **Treatment center studies (RADARS®, NAVIPPRO®)**
  - Survey instruments change over time

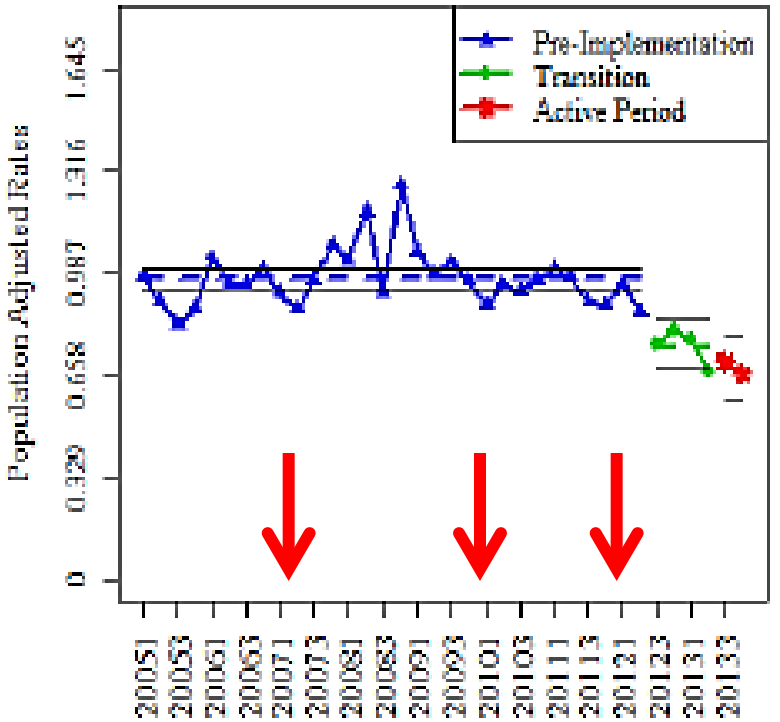
1. HealthCore Integrated Research Database

Limited Generalizability

Example: Washington State overdose death trends

- State opioid prescribing guidelines (2007, 2010)[1]
- Statewide legislation restricting high-dose opioid prescribing (2012)[2]

Population rates for overdose deaths involving opioids with an ER/LA formulation, Washington State Medical Examiner Study

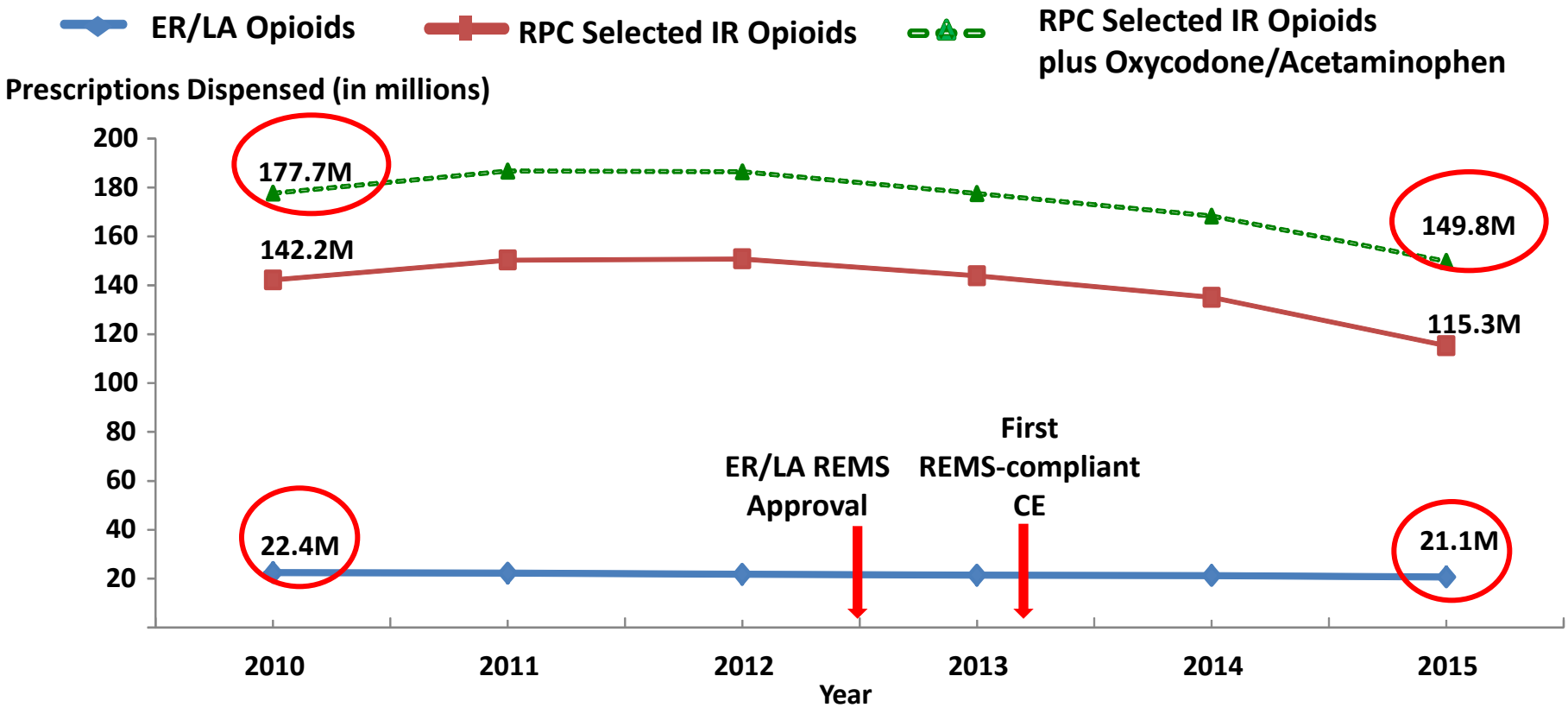


1. Interagency Guideline on Prescribing Opioids for Pain, Washington State Agency Medical Directors/ Group, 3rd Edition, June 2015
2. Washington State Department of Health: Medical Commission, Pain Management Resources

Interpretation of the Drug Utilization Data

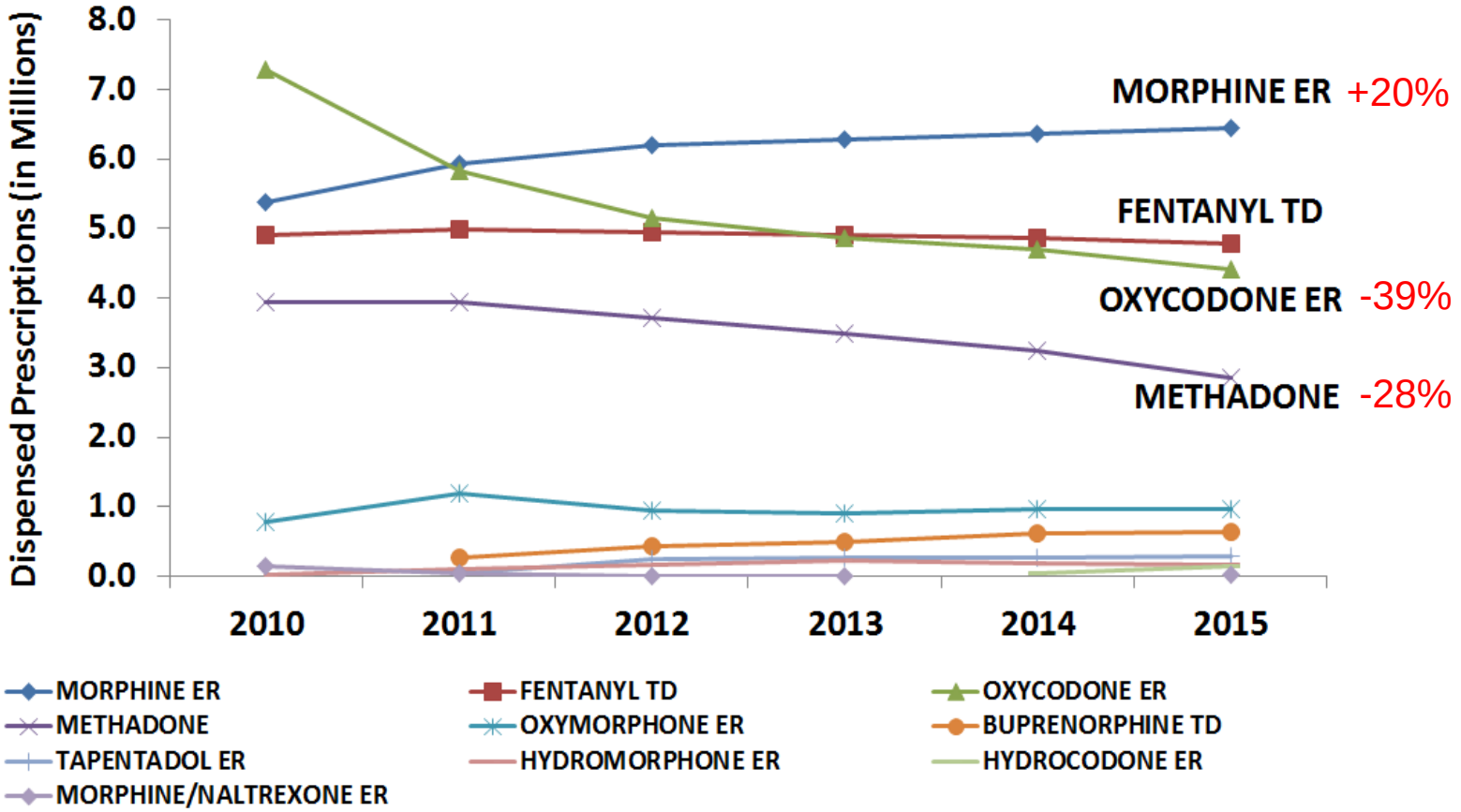
ER/LA and IR Opioid* Prescription Volume Declining

Nationally estimated number of prescriptions dispensed for ER/LA opioids and selected IR opioid products from U.S. Outpatient Retail Pharmacies , Years 2010-2015



* IR opioid prescription data provided by the REMS Program Companies (RPC), shown in red, did not include oxycodone/acetaminophen products. Above analyses conducted by FDA using IMS Health, National Prescription Audit™, extracted January 2016.

Trends In Prescription Volume Varied Across Individual ER/LA Opioids



Nationally Estimated Number of Dispensed Prescriptions for ER/LA Opioid Products from U.S. Outpatient Retail Pharmacies, by Molecule, 2010-2015
Source: FDA analysis of IMS Health, National Prescription Audit™. Extracted February 2016

Prescribing Behavior Analyses Difficult To Interpret

- **Examples**
  - Prescribing ER/LA opioids and doses indicated only for opioid tolerant patients to non-tolerant patients
  - ER/LA to IR opioid switching
  - Opioid-benzodiazepine concomitancy
  - Early refills
  - Change in prescribing volume by specialty
- **Limitations**
  - No information on clinical context—data tell us little about appropriateness of prescribing or patient access

Prescribing Behavior Analyses

- Example: Prescribing to opioid non-tolerant patients

	% prescribed to opioid non-tolerant patients (monthly mean)*		% change
	Pre-REMS	Active REMS	
Fentanyl TD	50.3%	49.5%	-1.7%
ER hydromorphone	48.9%	44.6%	-8.8%
ER morphine ≥ 90 mg	30.3%	29.4%	-2.9%

- Unknown how completely prescription history captured

Table based on data provided in the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report (analysis of IMS LRx data)

What do these surveillance studies tell us about changes in prescribing and safety outcomes?

Summary of Study Findings

- **ER/LA and IR opioid prescription numbers declining**
  - Follows more than a decade of increases
  - Fewer opioids available for misuse/abuse/overdose
  - Data say little about appropriateness of prescribing or patient access
- **Encouraging decreases in some adverse outcomes**
  - Decreases began prior to REMS launch
  - Seen for both ER/LA opioids and comparators
  - Many study limitations
  - *How to interpret in light of CDC data showing continued rise in national prescription opioid overdose death rates?*[1]

1. Rudd et al., *MMWR* January 2016

So…is the REMS making progress towards its goals?

Very difficult question to answer

- Evaluating the effectiveness of an intervention using observational data is inherently challenging
- Several factors contribute to this challenge here

Reach of REMS Intervention

- Absolute number of healthcare professionals who have participated in REMS-compliant training is large
- BUT, relatively small *proportion* (~20%) of ER/LA opioid prescribers have completed a REMS-compliant training
- Therefore, comparing overall prescribing or outcome rates across time periods would *underestimate effect of training on those who were trained, if training has an effect*
- Unknowns:
  - Training prescribers who most need it?
  - How many need to be trained to broadly impact clinical practice and population outcomes?
  - **Is it reasonable to expect to see measurable population-level changes yet?**

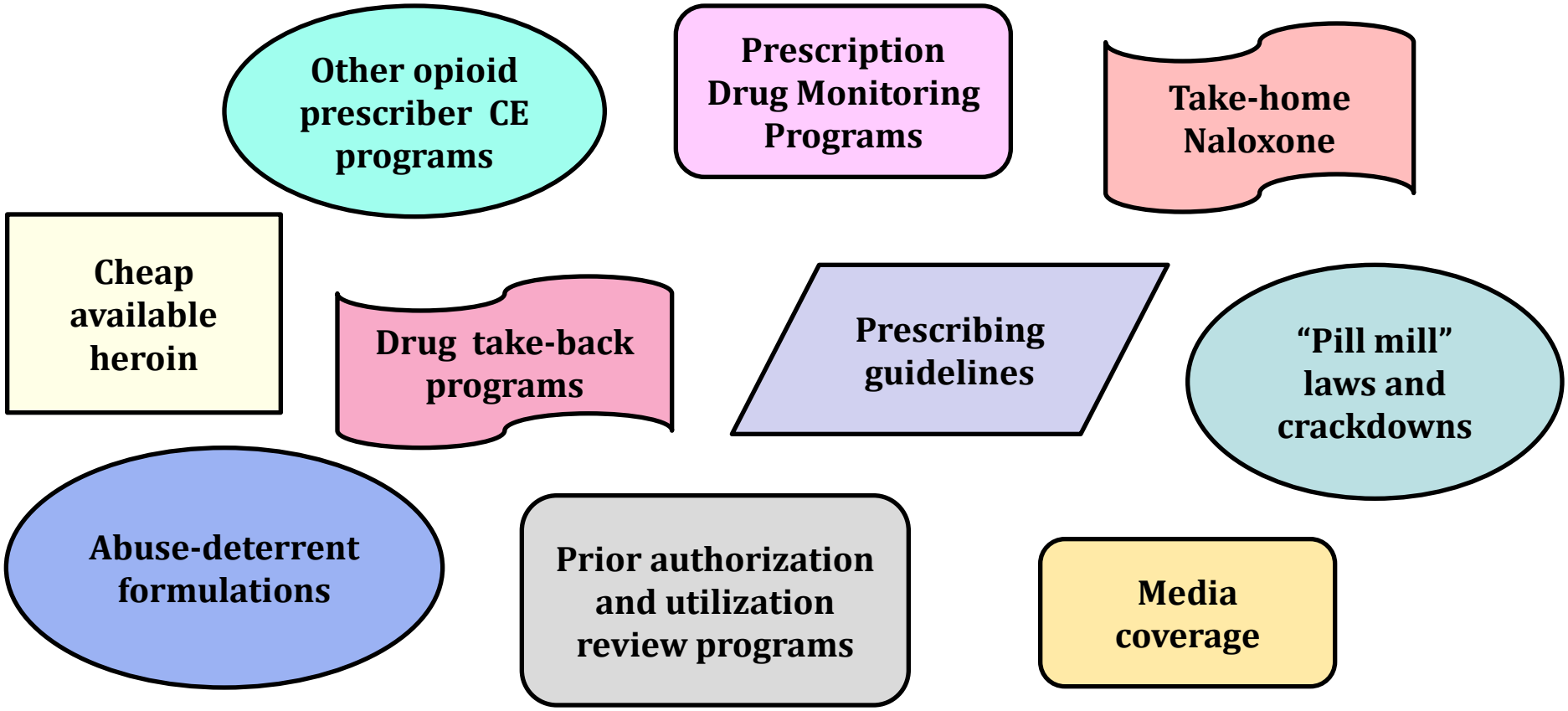
Complicated Path From Intervention To Measured Outcomes

- Even desirable changes in prescriber and patient behavior may have mixed effects on population outcome measures

Desired effects on prescriber/patient behavior		Possible effects on surveillance measures
Safer opioid storage and disposal— Fewer available for abuse	→ ↓	treatment center abuse rates
Improved recognition of abuse/addiction— more referrals to treatment	? → ↑	treatment center abuse rates
Safer opioid dosing and use	→ ↓	ED visit and poison center call rates?
Earlier recognition of overdose symptoms	? → ↑	ED visits and poison center call rates?

Other Efforts and Secular Trends

- Extremely difficult to isolate impact of REMS from many other interventions and secular trends since 2010
- Limited utility of comparator drugs—REMS could affect also



Conclusions

- Some findings are encouraging
- However,
  - Pathway from prescriber training to downstream outcomes is not straightforward
  - REMS just one component of large multifaceted response to a complex opioid crisis
- Surveillance studies do not tell us whether REMS is making progress towards its goals

Considerations for Future REMS Assessments

Monitoring Overall Trends In Opioid-Related Adverse Outcomes

- **Examples of other potentially useful data sources**
  - National surveys (non-medical use, opioid use disorder)
    - National Survey on Drug Use and Health
    - Monitoring the Future
  - CDC National Vital Statistics System (overdose deaths)
- **Limitations**
  - Cannot typically distinguish ER/LA from IR opioids
  - Long data lag times
- **Strengths**
  - More reliable trends
  - More generalizable

Directly Evaluating The Impact of REMS Training On Prescribing and Patient Outcomes

- **Would require novel study design**
  - Compare changes in prescribing/outcome measures for prescribers who complete REMS training to prescribers who do not
  - These data linkages are not readily available: would need prospective data collection
  - Need to select/operationalize/validate outcomes
  - Control for confounding: observational design/analysis methods adequate or need randomization?
- **Would such a study be feasible? Valuable?**

Thank you

Extended-Release and Long-Acting (ER/LA) Opioid Analgesic REMS 36-month Assessment: FDA Conclusions and Considerations for Next Steps

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Division of Risk Management
Center for Drug Evaluation and Research

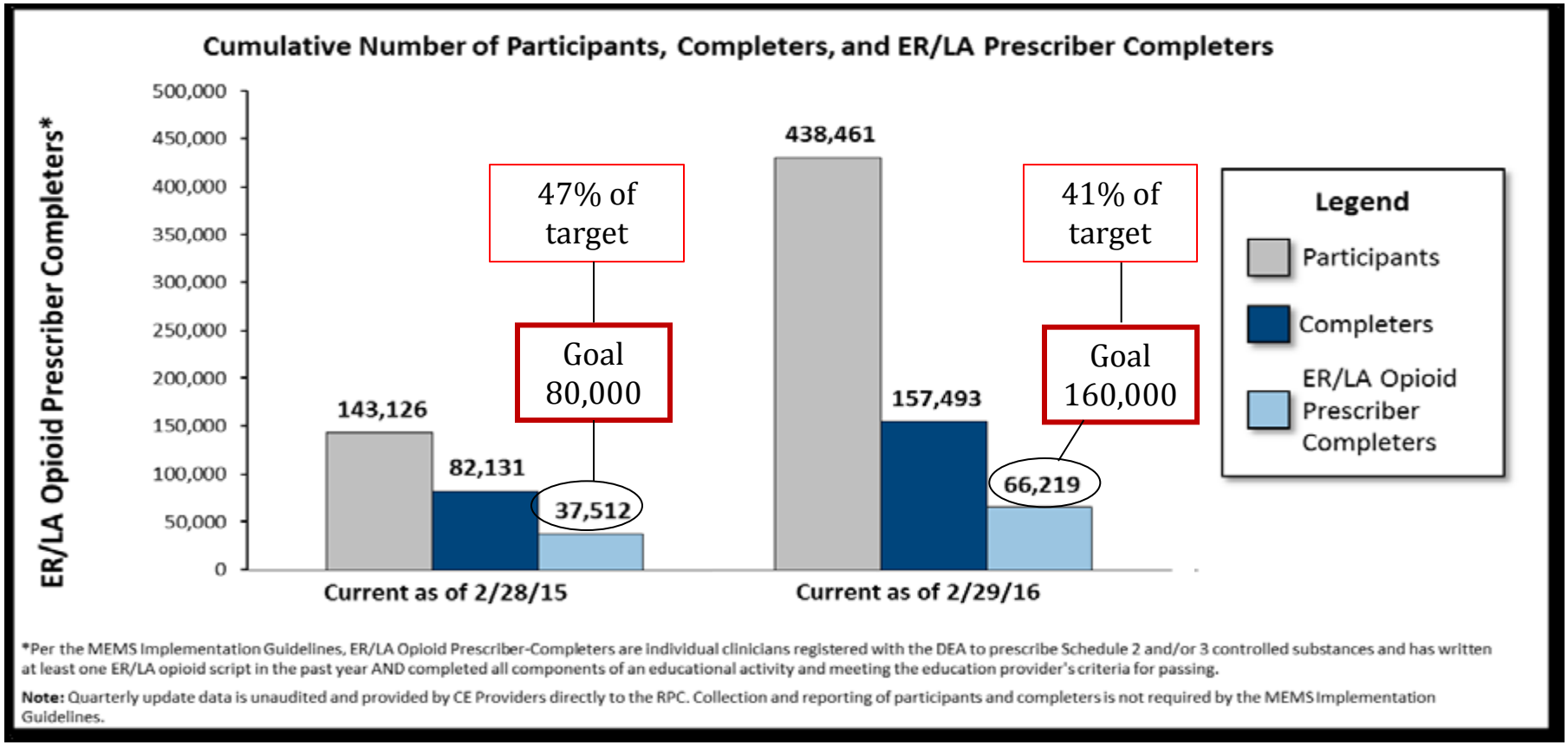
Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

May 3-4, 2016

REMS Goal

- To reduce *serious adverse outcomes* resulting from inappropriate prescribing, misuse, and abuse of ER/LAs while maintaining patient access to pain medications. Adverse outcomes of concern include *addiction*, *unintentional overdose*, and *death*

RPC Training Numbers



*Per the MEMS Implementation Guidelines, ER/LA Opioid Prescriber-Completers are individual clinicians registered with the DEA to prescribe Schedule 2 and/or 3 controlled substances and has written at least one ER/LA opioid script in the past year AND completed all components of an educational activity and meeting the education provider's criteria for passing.

Note: Quarterly update data is unaudited and provided by CE Providers directly to the RPC. Collection and reporting of participants and completers is not required by the MEMS Implementation Guidelines.

REMS-Compliant Training- FDA Conclusions

- A large number of health professionals have participated in or completed the training
  - Targets for prescriber training numbers have not been met
- Factors limiting uptake of training include:
  - voluntary nature
  - length of training (2-3 hours) & no “test-out”
  - sub-optimal REMS awareness
  - numerous competing trainings
- Prescriber definition misses new and institutional prescribers
- Health professional non-prescriber completers may be individuals involved in communicating safe use information to patients

REMS-Compliant Training-Considerations

- How much time to allow for a voluntary educational intervention to impact prescriber behavior?
- How many prescribers need to be trained & how much change in clinical practice is needed to see measurable effects on outcomes?
- Are the training goals/targets reasonable for a voluntary education program?
- How can we encourage more training uptake & completion?
- Do individuals who take a voluntary training differ from individuals who choose not to?
- Is it time to consider a form of mandatory training?
- Should training be tailored to specific prescriber types?
  - Specific needs of prescriber specialties; high-volume prescribers; low-volume prescribers.

Surveys – FDA Conclusions

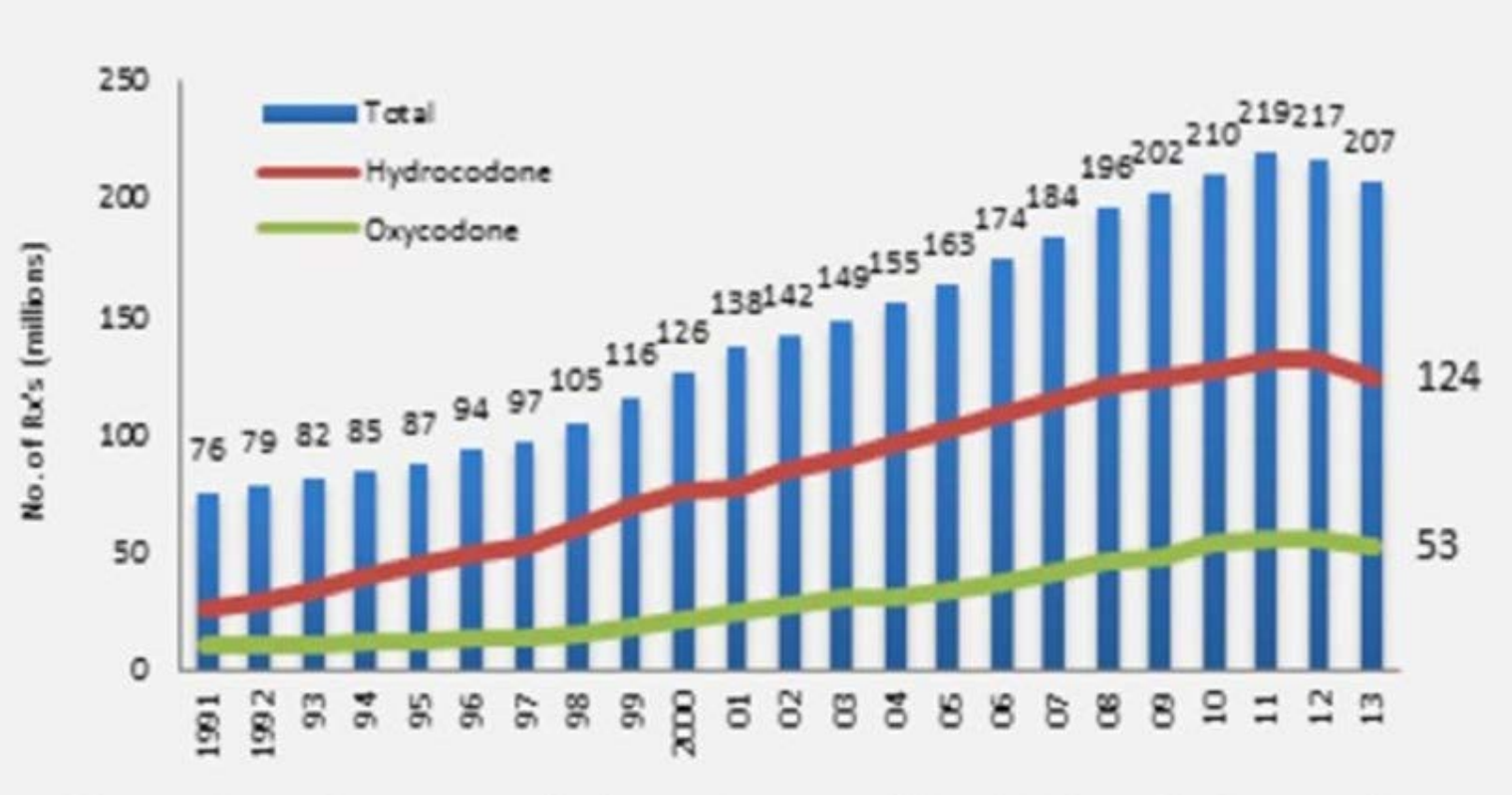
- Overall knowledge rates for most of the six areas of the FDA Blueprint were high for both prescribers and patients.
  - **Follow-up Prescriber Survey**: CE completers more frequently answered questions correctly.
  - **Prescriber Long-Term Evaluation Survey:** CE completers more often reported appropriate prescriber behaviors (risk counseling, screening patients for misuse/abuse).
  - **Patients:** Very good understanding of ER/LA risks
- Survey respondents not optimally representative of the general population of ER/LA prescribers and patients
  - Potential issues with comparability amongst studied groups
  - Convenience samples, self-selected, high non-response

Surveillance - FDA Conclusions

- Much of the provided surveillance data indicate decreases in some of the adverse events of interest.
- However, these data also indicate:
  - Decreases began to occur or had occurred before full REMS implementation
  - Decreases occurred in agents not subject to a REMS (IR opioids, benzodiazepines)
- Numerous federal, state, local, and health system related efforts to address opioid issues
- Surveillance sources utilized have significant limitations (e.g. convenience sampling)
- Overall – challenging to assess if and to what extent the REMS has contributed to the observed decreases.

Utilization - FDA Conclusions

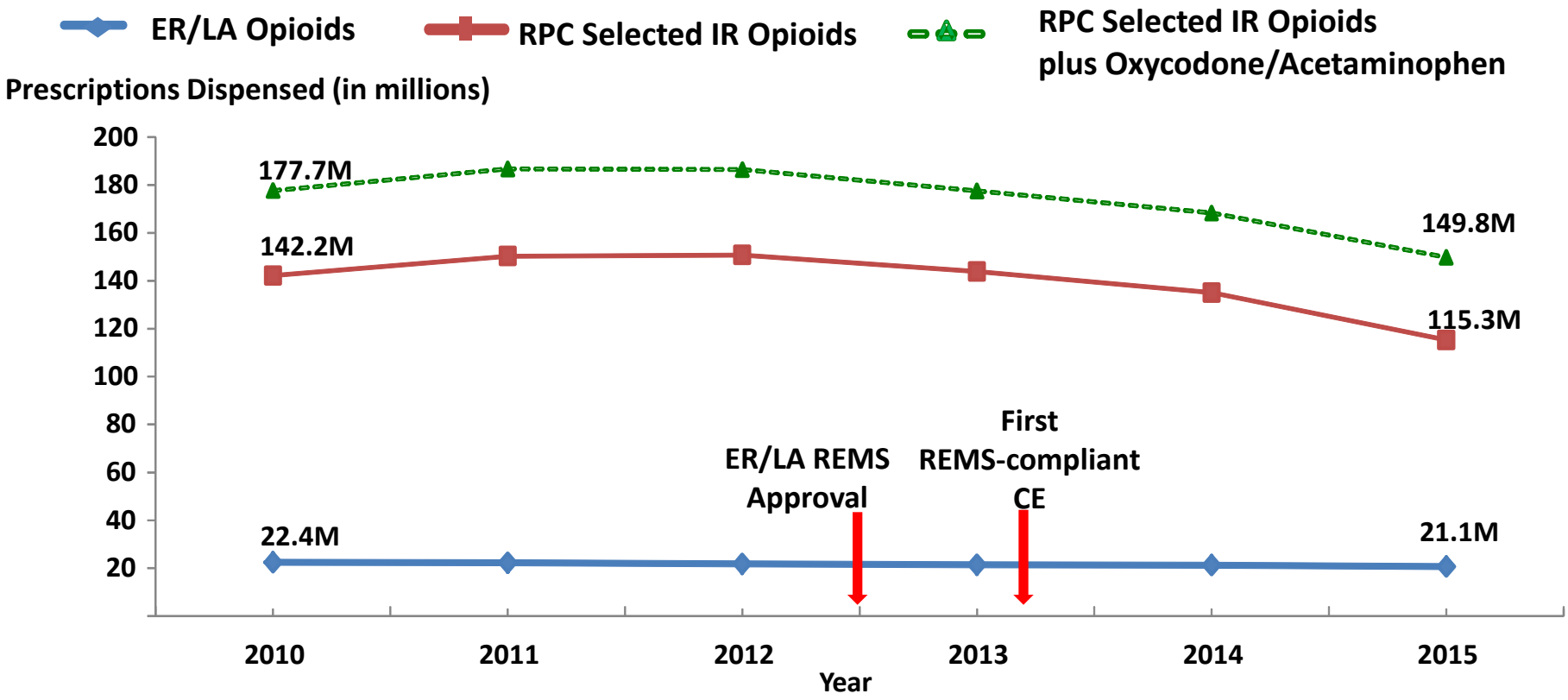
NIDA: All Opioid Prescriptions Dispensed by US Retail Pharmacies (millions)



From: **https://www.drugabuse.gov/**about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse

ER/LA and IR Opioid* Prescription Volume Declining

Nationally estimated number of prescriptions dispensed for ER/LA opioids and selected IR opioid products from U.S. Outpatient Retail Pharmacies , Years 2010-2015



* IR opioid prescription data provided by the RPC, shown in red, did not include oxycodone/acetaminophen products. Above analyses conducted by FDA using IMS Health, National Prescription Audit™, extracted January 2016.

Utilization - FDA Conclusions

- **F*ewer*** prescriptions dispensed for ER/LA opioids, IR opioids, and other comparators
  - Modest decrease should be viewed in light of the escalation in opioid prescribing over the previous years
  - ER/LA decreases appear to have started prior to full REMS implementation and driven mostly by decreases in oxycodone ER
- ***Decreases*** were also noted in ER/LA prescriptions written by most medical specialties from the pre-REMS to post-REMS period
  - Many of the decreases began prior to full REMS implementation
- ER/LA to IR opioid switch data & early prescription fill data difficult to interpret without knowing the "Why" (appropriateness)
- Prescription of opioids intended for use only in *opioid-tolerant* patients to many *opioid-**non**-tolerant* patients continues

Patient Access - FDA Conclusions

- To assess Patient Access, these data are provided:
  - Utilization data
  - Response to Patient & Prescriber Survey questions
- Utilization data do not directly inform this issue
- Responses to survey questions regarding access somewhat reassuring
  - Questions remain about the appropriateness of the survey populations
- Cannot tell whether the REMS has impacted patient access to ER/LAs based on these data
  - Those who could not get an ER/LA are not assessed

REMS Goals – FDA Overall Conclusions

- Summary of relevant findings:
  - Survey results indicate good overall knowledge and behaviors
    - prescribers who took the REMS-complaint training often did better
  - Surveillance data indicate decreases in some adverse events
- However, it is challenging to determine whether the REMS is meeting its goals due to:
  - Sufficient time for educational intervention to have an impact (?)
  - Inadequate data to inform burden/access
  - Limitations in the surveillance , utilization, and patient access data
  - Changes in surveillance/utilization findings pre-date the REMS and are seen in drug classes not subject to a REMS
  - Unknown reasons for decreases in surveillance outcomes and utilization metrics (judicious versus fear)
  - Difficulties in differentiating effects of the REMS from multitude of related efforts

Considerations for Next Steps

Does this REMS assure safe use?
Is it unduly burdensome?
Does it restrict patient access?

REMS Scope & Elements

- Revise Patient Materials
- Expand the Blueprint
  - Include info on management of pain, overdose, addiction
- Closed restricted program
  - Mandatory training
  - Prescriber, Pharmacy, Patient enroll
- Include IR opioids
- Other suggested modifications?

REMS Assessment Elements

- Different data sources to assess Surveillance and Utilization
- Alternate methodologies – studies of outcomes & behaviors in those trained vs. non-trained
  - *Challenging studies*
- Modify survey design/analysis
- Other suggested approaches?

THANK YOU

Considerations for Modifications to the ER/LA Opioid Analgesic REMS

Doris Auth, Pharm.D.
Team Leader, Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

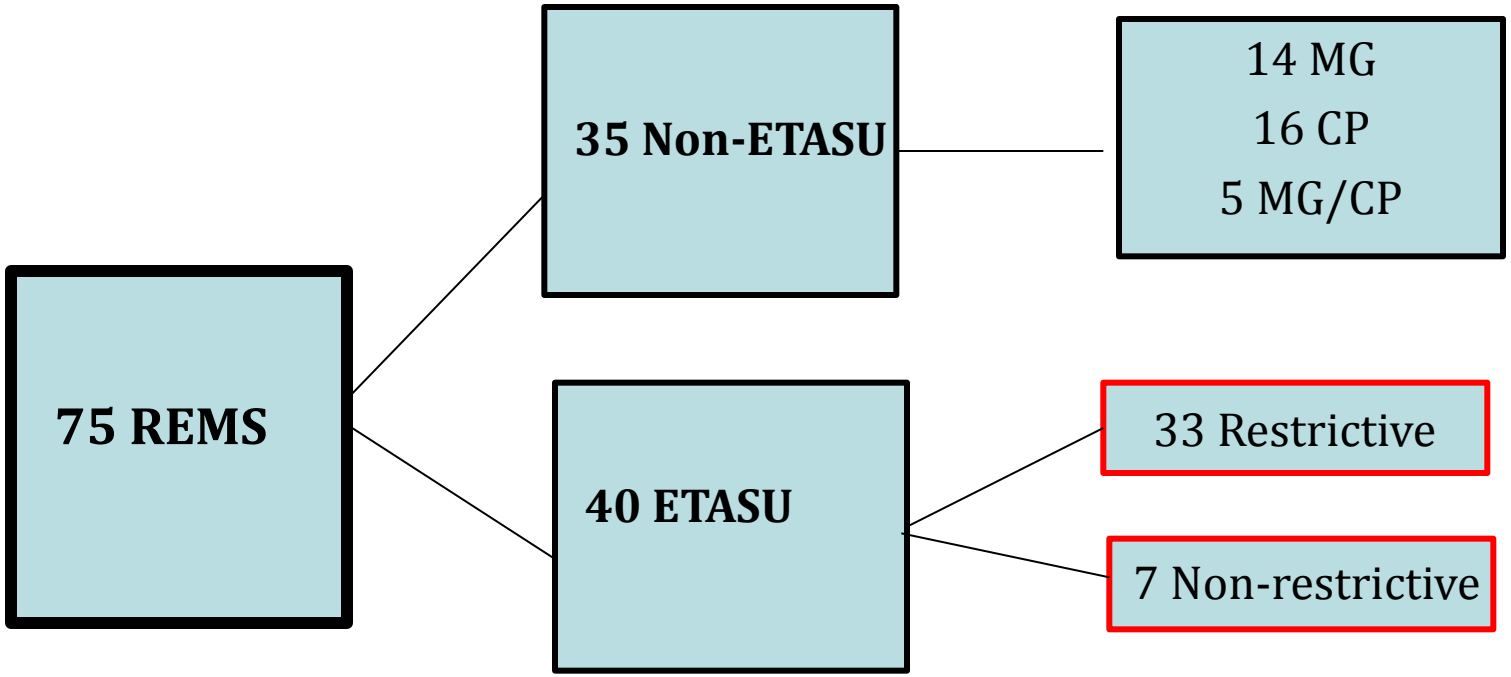
Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

May 3-4, 2016

Outline

- Overview of current Risk Evaluation and Mitigation Strategies (REMS) and participation in restrictive programs
- Options for modifications to ER/LA Opioid Analgesic REMS
- Program Examples
- Potential stakeholder impact in modified ER/LA Opioid Analgesic REMS
- Challenges and summary

Current REMS



ETASU REMS

Restrictive

- **Distribution/dispensing linked to**
  - **certification/training of prescribers,**
  - **certification of pharmacies and/or healthcare settings**
  - **enrollment of patients**
  - **documentation of safe use conditions**

Non-restrictive*

- **Application holders required to make training available to likely prescribers**

*ER/LA REMS

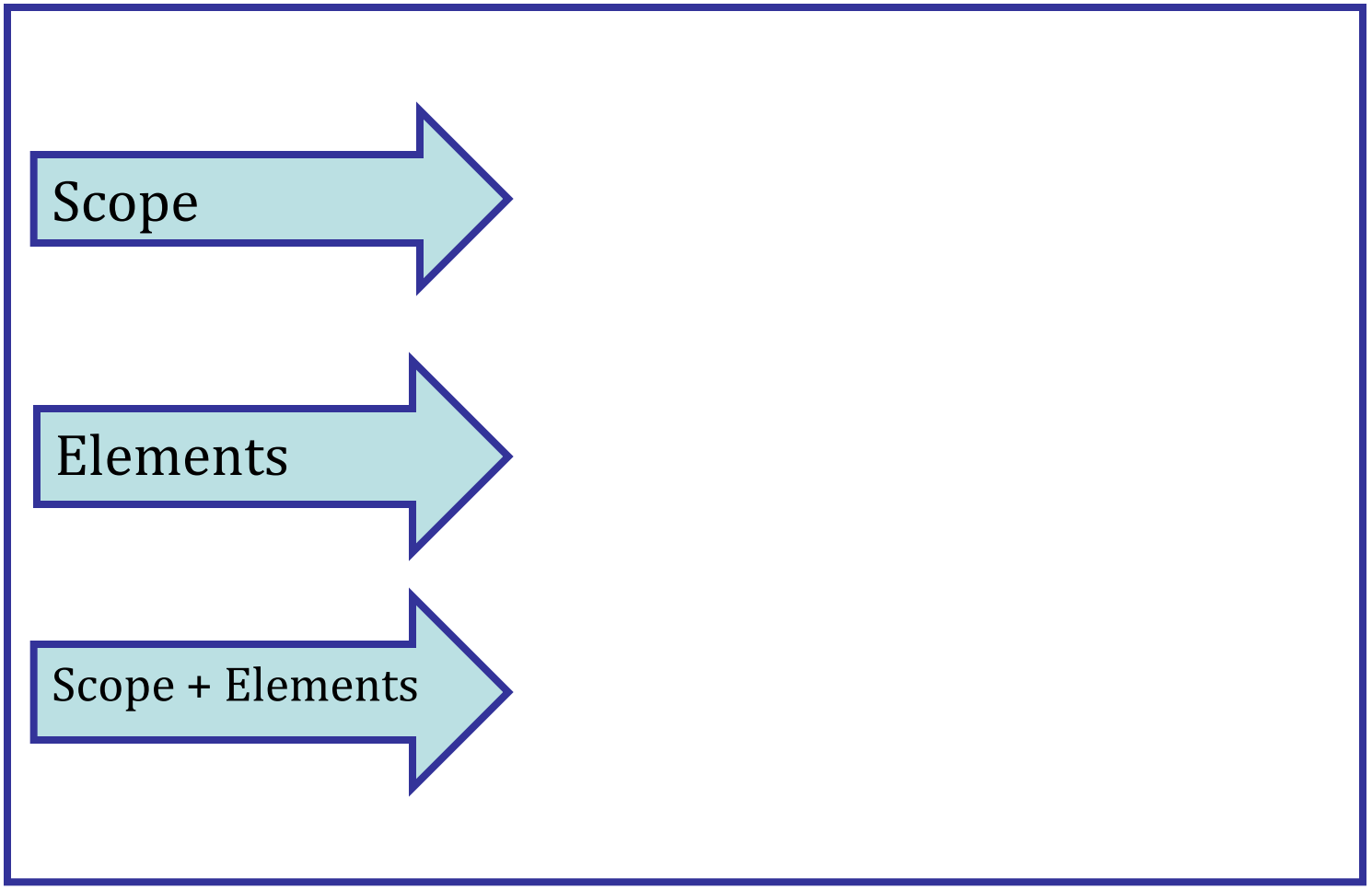
Stakeholder Participation In Restrictive REMS

- **Patients 75-235,000**
- **Prescribers 84-18,000**
- **Pharmacies 3-47,000**

60% of programs have less than 10,000 patients, 10,000 prescribers and 10,000 pharmacies participating

ER/LA OPIOID REMS MODIFICATION OPTIONS

ER/LA REMS Modification Options



ER/LA REMS Modification Options

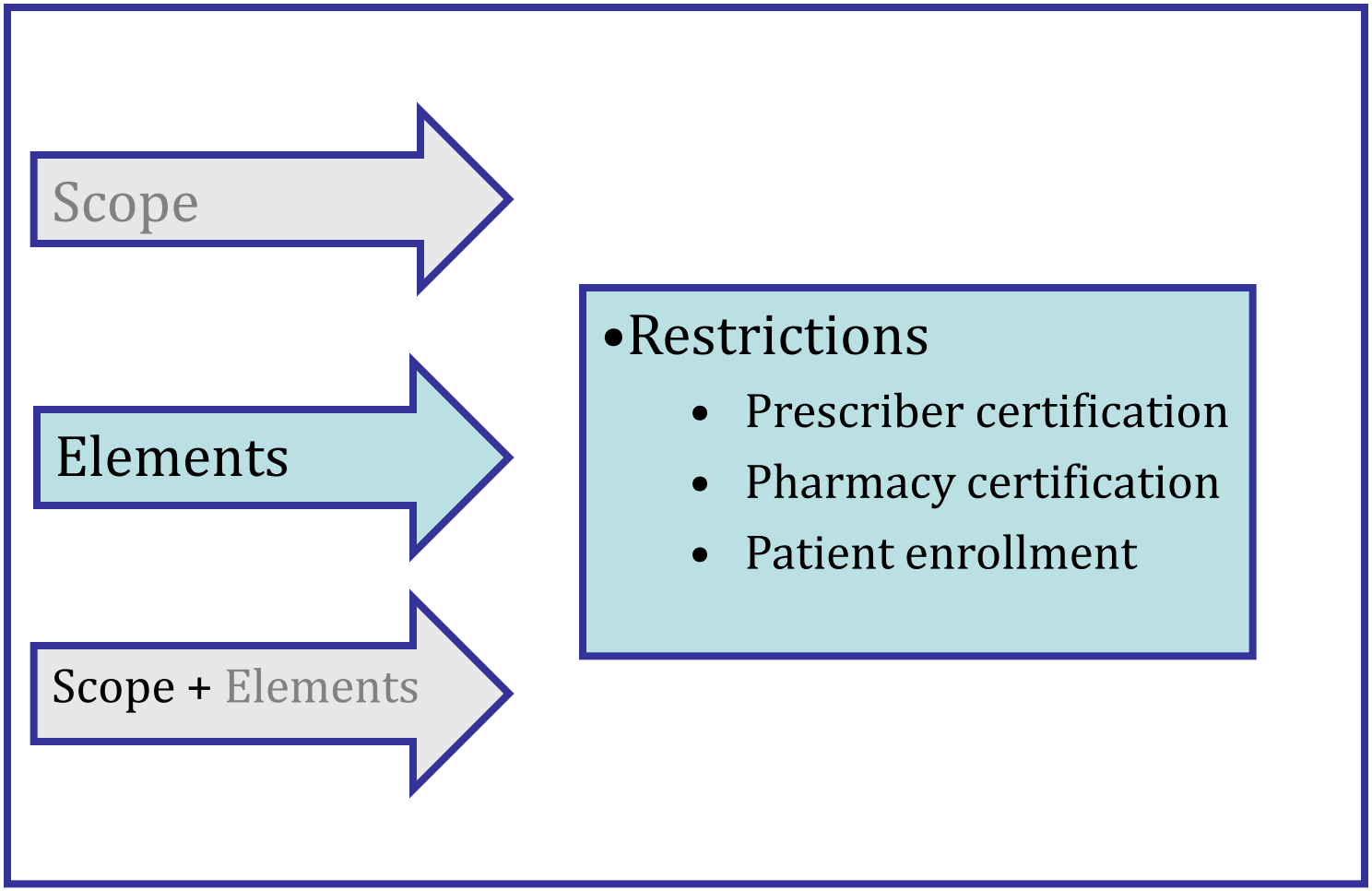
Scope

Elements

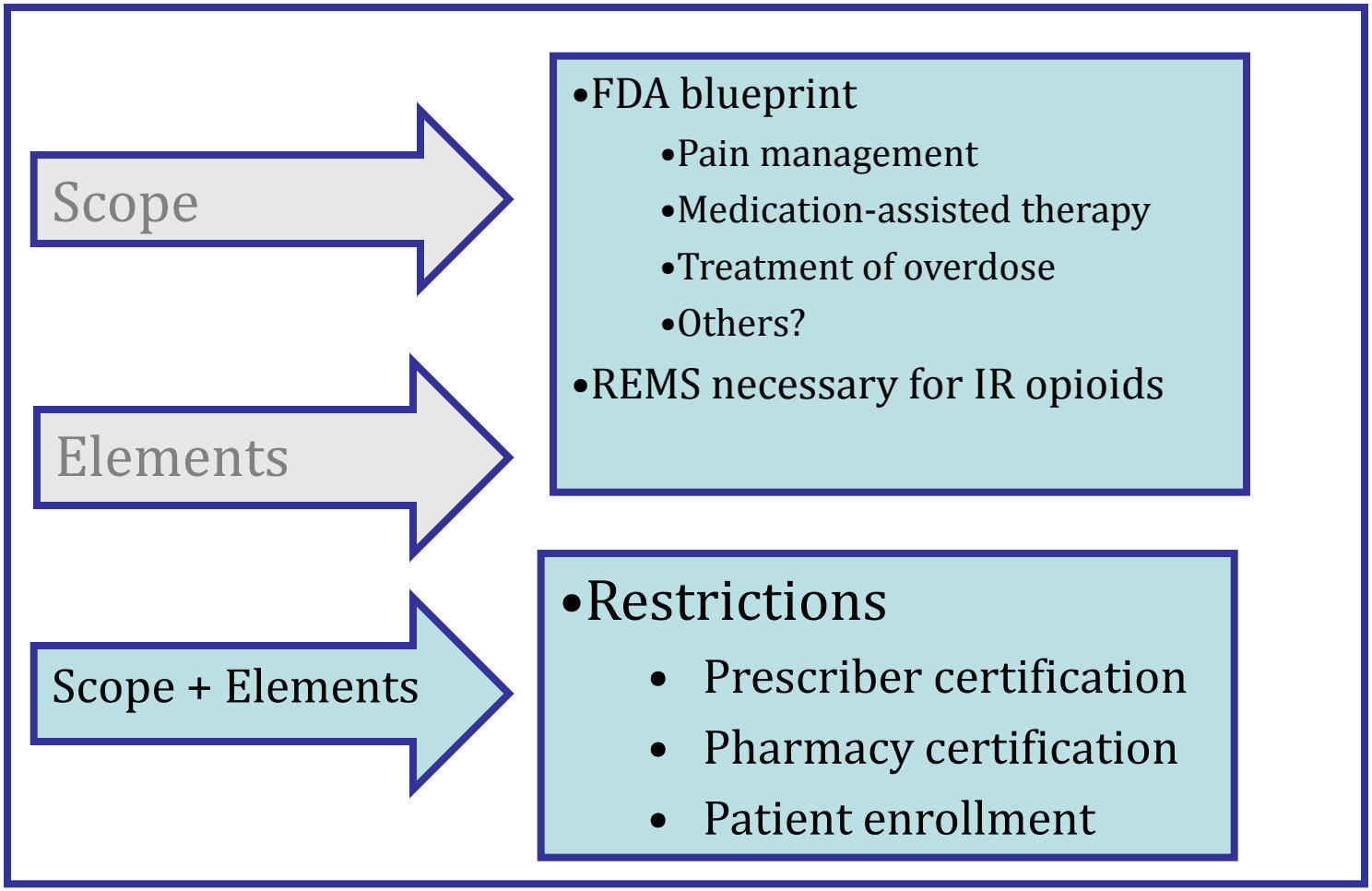
Scope + Elements

- FDA blueprint
  - Pain management
  - Medication-assisted therapy
  - Treatment of overdose
  - Others?
- Is a REMS necessary for IR opioids?

ER/LA REMS Modification Options



ER/LA REMS Modification Options



EXAMPLES – RESTRICTIVE REMS

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) and ISOTRETINOIN (iPLEDGE) REMS

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

- Shared-system REMS
  - Approved December 2011
  - 8 application holders
- Product Information
  - The formulations include a buccal film, buccal tablet, sublingual spray, and nasal spray of fentanyl citrate
  - Indicated for breakthrough pain in cancer patients 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
- REMS Goal
  - Mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

TIRF REMS Stakeholder Requirements

PRESCRIBER

- Review education program and complete knowledge assessment
- Counsel patient
- Complete Patient Prescriber Agreement (PPA) with patients

PHARMACY

- Review education program and complete knowledge assessment
- Passively enrolls patient
- Obtain authorization to dispense via claims adjudication (phone or fax for closed-systems)
- Provide patient with MG

PATIENT

- Complete PPA with prescriber
- Acknowledge understanding of risks, proper use, safe storage and disposal

Isotretinoin (iPLEDGE) REMS

- Shared-system REMS
  - Approved 2005
  - 6 application holders
- Indicated for severe recalcitrant nodular acne
- REMS risks
  - Human teratogen
- REMS goals
  - Prevent fetal exposure and educate prescribers and patients and pharmacies about the serious risks and safe use conditions

iPLEDGE REMS
Stakeholder Requirements

PRESCRIBER

- Review educational material and complete enrollment
- Counsels and complete informed consent (IC) with patient
- Enrolls patient by appropriate risk category
- Document safe use conditions for Females of Reproductive Potential each month (pregnancy test and contraceptive choices)

PHARMACY

- Review educational material and complete enrollment
- Provide patient with MG
- Obtain and document authorization
  - Via web or phone
- Dispense no more than 30 days supply

PATIENT

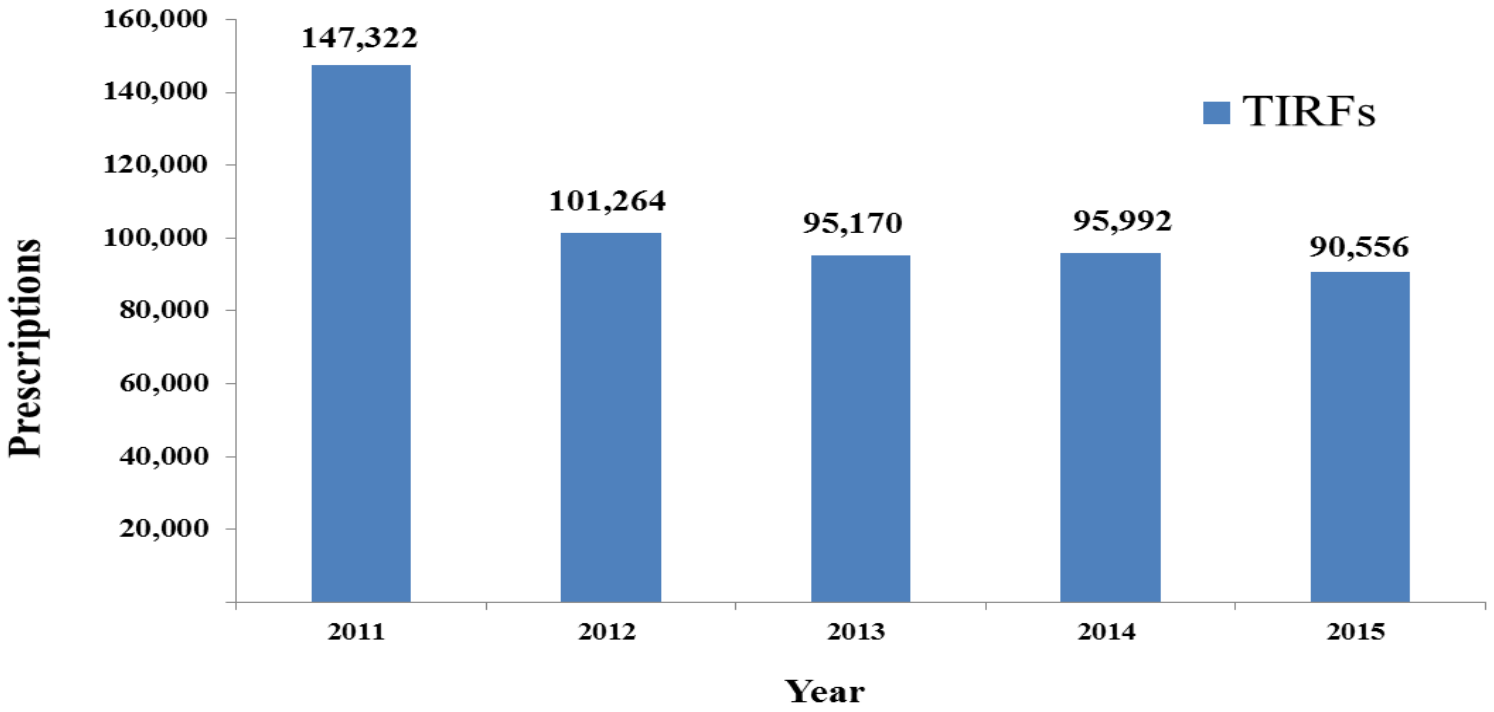
- Complete Informed Consent
- Females of reproductive potential
  - Pre-treatment and monthly pregnancy tests
  - Completion of monthly comprehension questions

Stakeholders Impacted

REMS program	Active prescribers	Active outpatient/ specialty pharmacies	Active patients
TIRF Shared REMS (2015)	9096	42,316	8740*
Isotretinoin Shared REMS (2015)	18,461	46,726	234,622
ER/LA Opioid	320,000	67,000	
ER/LA and IR Opioid	1.5 million	67,000	

*New patients only

TIRF Products

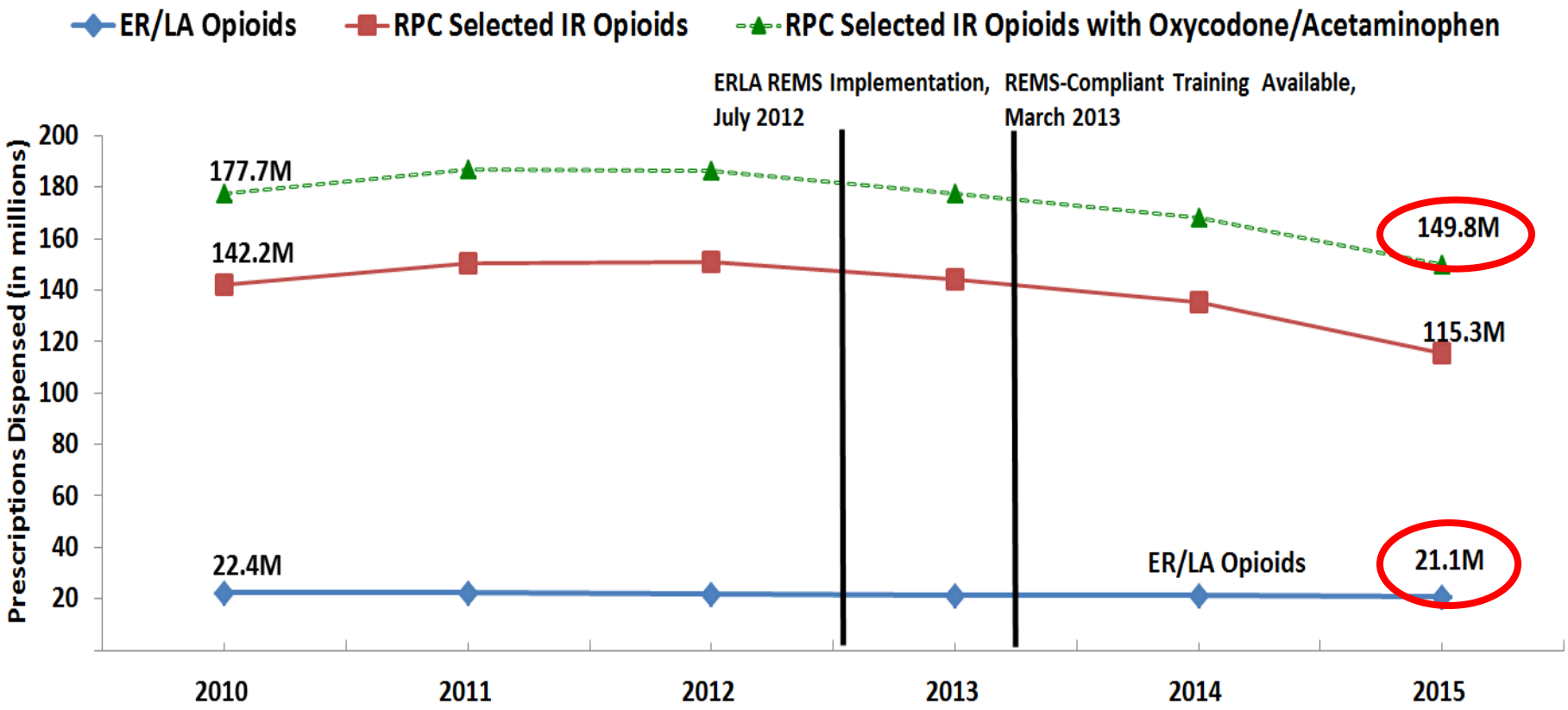


Nationally estimated number of prescriptions dispensed for TIRFs* from U.S. outpatient retail pharmacies

**TIRFs include: Abstral, Actiq, Fentanyl Citrate (generic), Fentora, Lazanda, Onsolis, Subsys*

- *Source: IMS Health, National Prescription Audit ™ Extracted March 2016*

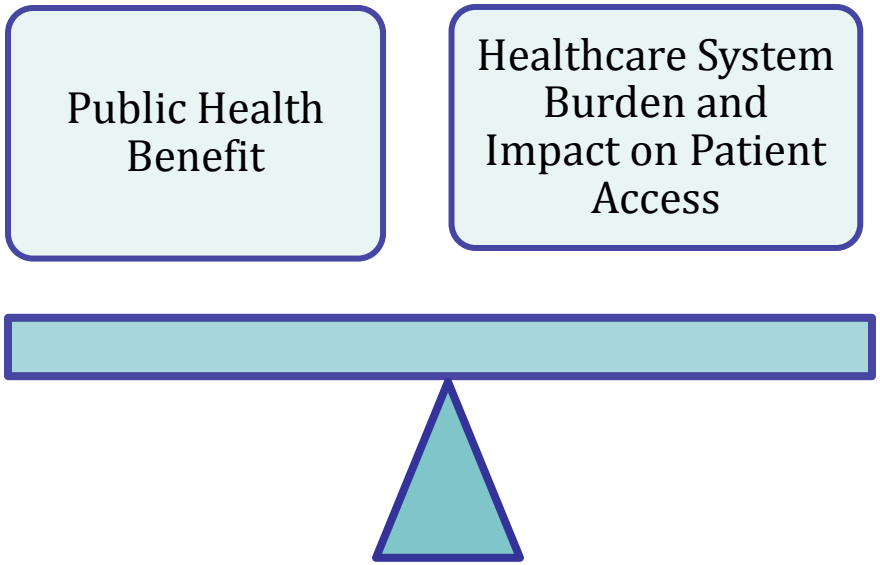
Drug Use Patterns



Nationally estimated number of prescriptions dispensed for ER/LA opioids and selected IR opioid products from U.S. Outpatient Retail Pharmacies , Years 2010-2015

FDA analysis of IMS Health, National Prescription Audit™. Extracted January 2016

Summary


Public Health Benefit
Healthcare System Burden and Impact on Patient Access

	ER/LA Opioid Analgesics				IR Opioids			
PRESCRIBING SPECIALTY	Pre-Implementation	Active Period	Pre-Implementation vs Active Period		Pre-Implementation	Active Period	Pre-Implementation vs Active	
	Mean	Mean	P-Value (T-Test)	% Change	Mean	Mean	P-Value (T-Test)	% Change
PCP	2,247,878	1,937,431	**0.000**	**-13.80%**	14,125,269	12,550,022	**0.010**	**-11.20%**
Anesthesiology	535,470	550,548	**0.006**	**2.80%**	947,253	1,054,778	**0.001**	**11.40%**
Pain	547,007	544,796	0.578	**-0.40%**	933,032	1,003,309	**0.003**	**7.50%**
Nurse Practitioners	398,836	533,252	**0.000**	**33.70%**	1,693,955	2,142,838	**0.000**	**26.50%**
Physical Medicine & Rehabilitation	500,474	489,899	**0.008**	**-2.10%**	1,051,678	1,084,609	**0.157**	**3.10%**
Physician Assistant	330,397	433,601	**0.000**	**31.20%**	2,024,547	2,455,599	**0.000**	**21.30%**
All Other	331,031	277,754	**0.003**	**-16.10%**	4,740,801	4,745,099	**0.896**	**0.10%**
Oncology	182,579	160,393	**0.000**	**-12.20%**	428,891	389,870	**0.007**	**-9.10%**
Surgery	172,264	136,722	**0.000**	**-20.60%**	5,541,767	4,653,964	**0.005**	**-16.00%**
Neurology	156,476	129,092	**0.000**	**-17.50%**	506,771	432,556	**0.004**	**-14.60%**
Rheumatology	84,800	73,176	**0.000**	**-13.70%**	479,871	436,806	**0.009**	**-9.00%**
Pediatrics	37,496	31,669	**0.000**	**-15.50%**	318,218	276,697	**0.004**	**-13.00%**
Emergency	41,449	30,861	**0.000**	**-25.50%**	2,348,030	1,971,420	**0.000**	**-16.00%**
Hospice and Palliative Medicine	4,583	4,314	**0.012**	**-5.90%**	7,015	6,046	**0.000**	**-13.80%**
Dentist	4,942	2,545	**0.000**	**-48.50%**	2,742,677	2,498,975	**0.051**	**-8.90%**