Extended-Release and Long-Acting (ER/LA) Opioid Analgesic REMS

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Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics-Exploring the Path Forward; Public Workshop
May 9-10, 2017

Overview

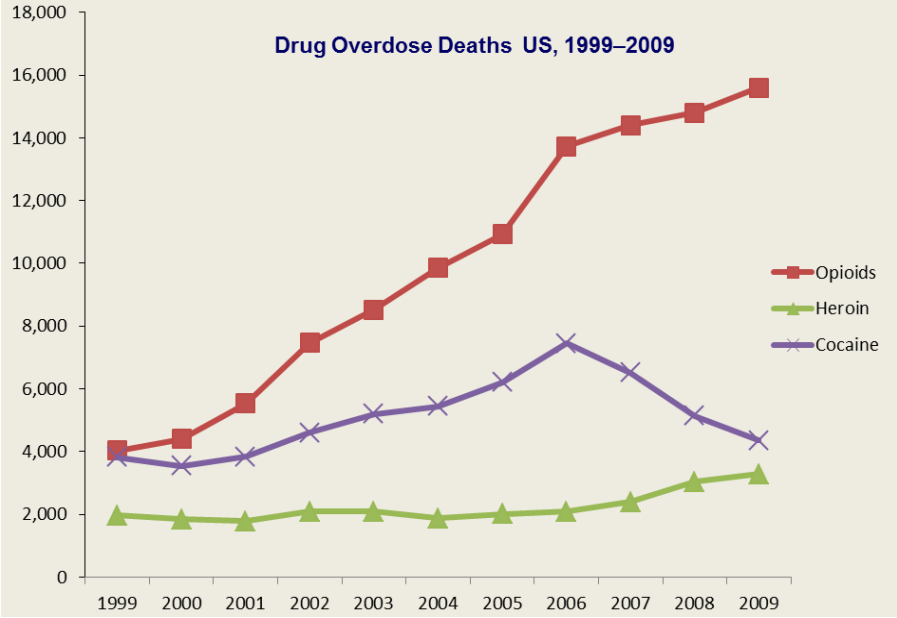
- Background on risk management of ER/LA opioid analgesics and Risk Evaluation and Mitigation Strategies (REMS)
- ER/LA Opioid Analgesics REMS
- Recommendations from the May 3-4, 2016 Joint DSaRM and AADPAC Meeting
- Update on the status of the ER/LA Opioid Analgesics REMS

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

History of ER/LA Opioid Analgesics Risk Management

- In early 2000s, FDA first received reports of problems with prescription opioid abuse especially involving modified release formulations
  - crushing of the tablet to defeat the extended-release (ER) properties
  - misuse by several different routes
  - addiction, overdose and death

- Despite adding warnings to product labeling and developing risk management plans to address inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics– drug overdose deaths resulting from opioids continued to increase.



Source: National Vital Statistics System

History of ER/LA Opioid Analgesics Risk Management

- In 2009, FDA notified manufacturers of ER/LA opioid analgesics that their products would require a REMS to ensure the benefits outweigh the risks
- Between 2009-2011 FDA obtained stakeholder input on the development of a REMS for these products (4 public meetings, 1 advisory committee meeting, and public docket)
- This would be the largest REMS to-date, as such FDA considered
  - scope of the REMS
  - impact on the health care system
  - impact on patient access

Some Highlights of Stakeholder Comments

- If the REMS only applies to ER/LA opioid analgesics, there will be shifts in prescribing to immediate release (IR) opioid analgesics.
- Support for prescriber education
  - Some supported mandatory training but felt it would be best accomplished if linked to DEA registration or through the state medical boards.
  - Stakeholders felt that real-time verification of training before filling an opioid prescription could cause some prescribers to “opt out” of the program
- Patient education is important but patient enrollment would be overly burdensome, create a stigma, and may adversely affect patient access.

REMS Background

- A REMS is a required risk management plan that utilizes risk mitigation strategies beyond FDA-approved professional labeling
- Food and Drug Administration Amendments Act of 2007 provided FDA the legal authority to require a REMS for applicable drugs*
  - Pre-approval, if FDA determines a REMS is needed to ensure the benefits of the drug outweigh the risks
  - Post-approval, if FDA becomes aware of new safety information and determines that a REMS is necessary
- REMS are developed and implemented by the drug manufacturers

* Section 505-1 of Food, Drug, and Cosmetic Act (FDCA)

Components of a REMS

- A REMS can include
  - Medication Guide or Patient Package Insert (PPI)
  - Communication Plan for Health care Providers (HCPs)*
  - Elements to Assure Safe Use
  - 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 HCPs who prescribe the drug(s)
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug in certain health care settings (e.g., hospitals)
- Drug is dispensed/administer 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

- **Components of a REMS are linked to distribution/dispensing the drug**
  - **certification/training of prescribers**
  - **certification of pharmacies and/or healthcare settings**
  - **documentation of safe use conditions**

Non-restrictive

- **Components of a REMS are not linked to distribution/dispensing the drug**
  - **manufacturers are required to make training available to likely prescribers**

ER/LA Opioid Analgesics REMS

- REMS was approved by FDA on July 9, 2012
- A shared system REMS
  - 38 Sponsors comprise the ER/LA REMS Product Companies
  - Includes approximately 67 applications (NDA and ANDA)
  - Active ingredients:

Buprenorphine	Fentanyl	Tapentadol
Hydrocodone	Hydromorphone	Methadone
Morphine	Oxycodone	Oxymorphone

Goal of the REMS

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

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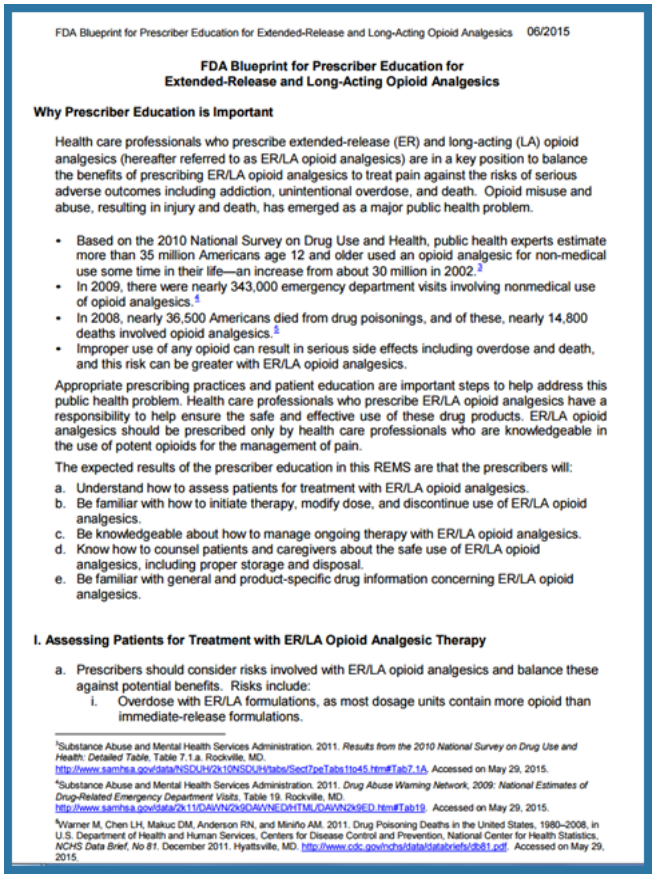
Components of the ER/LA Opioid Analgesics REMS

- Prescriber Training – Primary component
- Patient materials
  - Medication Guide
  - Patient Counseling Document
- Letters to targeted prescribers, professional organizations, and licensing boards
- Call Center and Website
- Assessments of the effectiveness of the REMS

Prescriber Training

- Manufacturers are required to make training available to prescribers of ER/LA opioid analgesics
  - They are meeting this obligation by providing unrestricted grants to continuing education (CE) providers to develop CE based upon the FDA Blueprint
- Non-restrictive ETASU (defined earlier)
  - 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

FDA Blueprint



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.

- Posted on the FDA website for accredited CE providers to develop training
- Focuses on safe prescribing of ER/LA opioid analgesics
- Includes the following domains:
  1. Assessing patients for treatment
  2. Initiating therapy, modifying dosing and discontinuing use
  3. Managing therapy
  4. Counseling patients and caregivers about the safe use
  5. General drug information
  6. Specific drug information
- REMS-compliant training:
  - Offered by an accredited CE provider
  - Includes all elements in the FDA Blueprint
  - Includes a knowledge assessment
  - Is subject to independent audit to confirm that conditions of the REMS training have been met

https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf

Prescriber Training Performance Targets

In 2012, FDA estimated the total number ER/LA opioid analgesic prescribers at 320,000

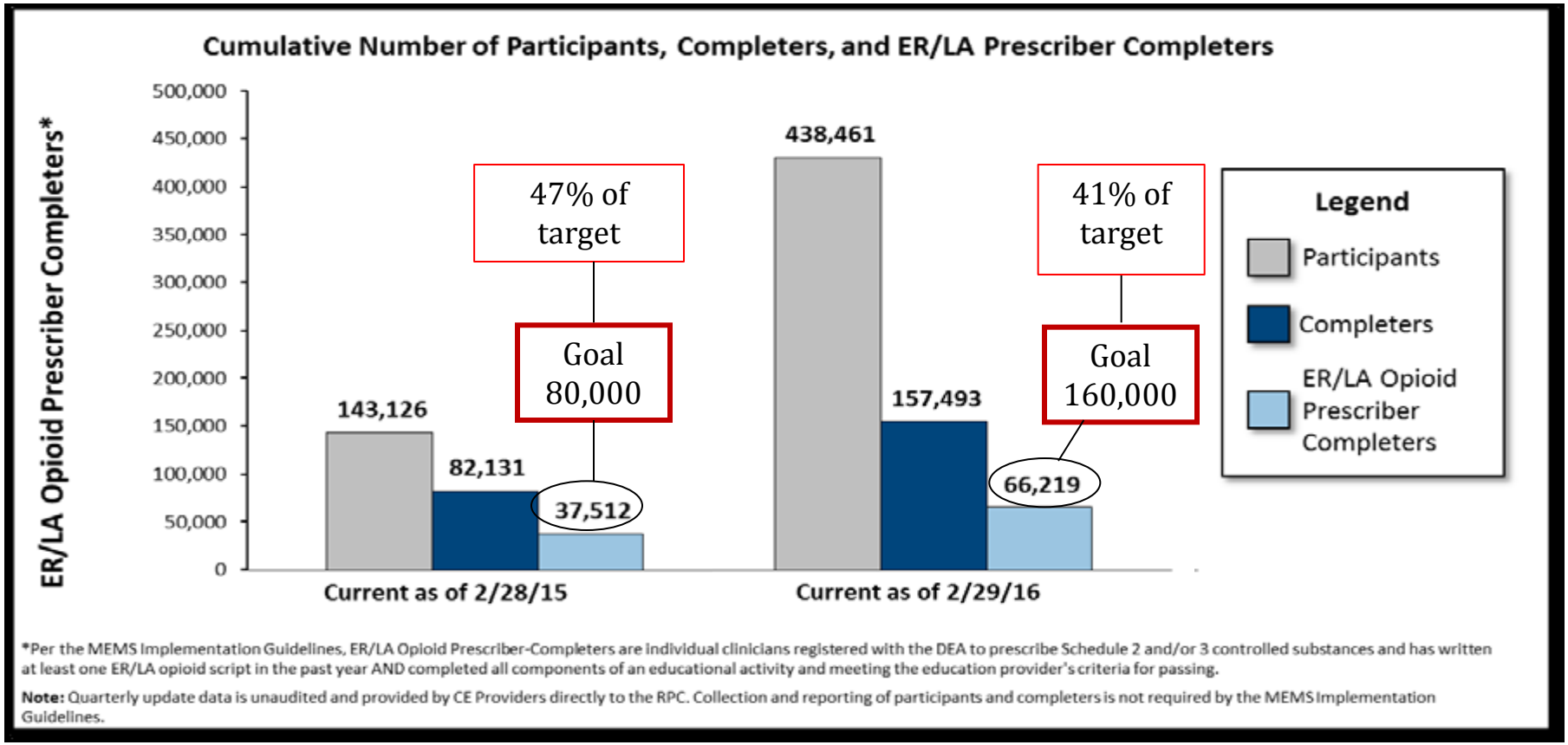
Date	Year	Training Target	Percent
March 2013 (CE became available)	0		
March 2015	2	80,000	25%
March 2016	3	160,000	50%
March 2017	*4*	*192,000*	*60%*

REMS Assessments*

- Number of ER/LA opioid analgesic prescribers who completed REMS-compliant training
- Independent audit of the quality and content of the educational programs
- Results of prescriber and patient surveys
- Surveillance studies- key safety outcomes
- Drug utilization patterns
  - Changes in prescribing behavior
  - Evaluation of patient access

*Only high level findings are presented. Comprehensive assessment findings are available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm

REMS-Compliant Training Numbers*



*Data presented at the Joint DSaRM and AADPAC Meeting May 3-4, 2016

HCP Participants in REMS-Compliant Training

- Over 400, 000 HCPs participated in or completed REMS CE training, many of which were not prescribers targeted for the education.
  - These numbers are impressive for a program that is voluntary
- The reason that ER/LA opioid analgesics prescriber targets were not met is not entirely clear, possibilities include:
  - Multiple sources of education on opioids; some mandated by states or employers
  - Scope of the training was narrowly focused on ER/LAs
  - Not required in order to prescribe

Summary of Other Assessment Findings

Assessment Metric	Findings	Comments
Audits	All of the audited CE programs met requirements for content, accuracy and assessment.	About 1/3 of the audited CE programs failed to prominently display financial disclosure; all were remediated
Surveys	Overall knowledge rates for most of the six areas of the FDA Blueprint were high for both prescribers and patients.	Methodological issues affected representativeness of respondents; may not reflect general population of ER/LA OA prescribers and patients
Surveillance Studies	Surveillance data suggested possible decreases in some of the adverse events of interest	-Decreases began before REMS implementation and in products not subject to a REMS -Surveillance sources utilized have significant limitations for evaluating program impact (e.g. convenience sampling)

Summary of Other Assessment Findings

Assessment Metric	Findings	Comments
Drug Use	Fewer prescriptions written by most medical specialties for OA.	Drop in prescriptions started prior to full REMS implementation. Not possible to determine “Why” (appropriateness)
Patient Access	Cannot tell from drug use and survey data whether the REMS has impacted patient access to ER/LA OAs	Those who could not get an ER/LA are not assessed

Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

- Meeting was held on May 3 and 4, 2016 to obtain input on whether the REMS is meeting its goals
  - key assessment findings were presented
- FDA also sought input from the committees on:
  - alternative methodologies for evaluating the program
  - whether the FDA Blueprint should be revised and/or expanded;
  - whether to expand the REMS program to include IR opioid analgesics; and
  - whether additional modifications should be made to the REMS

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm

Advisory Committee Recommendations

The majority of the committee members recommended:

1. Extend REMS requirements to the IR opioid analgesics

2. Broaden education to include pain management and extend the training to other HCPs involved in the management of patients with pain

3. Integrate the REMS education with mandatory education provisions

Update on the status of the ER/LA Opioid Analgesic REMS

- Extending REMS requirements to the IR opioid analgesics
  - FDA invited all affected applicant holders to a meeting on January 25, 2017, to inform them of the Agency's intention to require a REMS for IR*, ER, and LA opioid analgesics and to discuss strategies for developing an expanded REMS that includes all applicant holders.

* Excludes Transmucosal Immediate-Release Fentanyl products and Buprenorphine Transmucosal Products for Opioid Dependence subject the separate REMS requirements and IV opioid analgesics intended for administration under supervised settings.

Update on the status of the ER/LA REMS

- Updating the Blueprint
  - FDA has been revising the blueprint to include pain management and the safe use of opioid analgesics and is exploring mechanisms to extend the training to other HCPs involved in the management of patients with pain.
  - FDA is establishing a public docket to seek comment on the draft revisions to the Blueprint. The draft Blueprint is available at https://www.fda.gov/Drugs/NewsEvents/ucm538047.htm

Outline of Draft Revisions to the Blueprint

Section 1: The Basics of Pain Management

I. DEFINITIONS AND MECHANISMS OF PAIN

II. ASSESSING PATIENTS IN PAIN

Section 2: Creating the Pain Treatment Plan

I. COMPONENTS OF AN EFFECTIVE TREATMENT PLAN

II. NONPHARMACOLOGIC THERAPIES

III. GENERAL PRINCIPLES OF PHARMACOLOGIC ANALGESIC THERAPY

- A. Non-opioid analgesics and adjuvant medications
- B. Opioid analgesics

IV. MANAGING PATIENTS ON OPIOID ANALGESICS

- A. Initiating treatment with opioids – acute pain
- B. Initiating treatment with opioids – chronic pain
- C. Periodic review and monitoring for patients on opioid analgesics
- D. Long-term management
- E. When to consult with a pain specialist
- F. Medically directed opioid tapering
- G. Importance of patient education

V. ADDICTION MEDICINE PRIMER

Summary

- The ER/LA Opioid Analgesics REMS was implemented in 2012 to address the growing epidemic of opioid abuse, addiction and overdose.
- FDA intends to modify the ER/LA Opioid Analgesic REMS after evaluating existing requirements and considering recommendations from the joint meeting of the DSaRM and AADPAC and the public to include the IR opioid analgesics and to revise the Blueprint.
- This public meeting will inform next steps on how best to implement training for opioid analgesic prescribers.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