Background on the Opioid Analgesics REMS

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What is a REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

- *REMS may include a number interventions to help reduce the occurrence and/or severity of certain serious risks*
- *FDA has the authority to require a REMS before approval or post approval if FDA becomes aware of new safety information.*
- *FDA must consider a number of factors before requiring a REMS.*

Additional key points about REMS

- Drug sponsors design and develop REMS programs, FDA reviews and approves them
- Drug sponsors are required to conduct and submit assessments of the REMS and FDA reviews them to determine if the REMS is meeting its goals
- REMS programs can be designed for a single drug or a class of drugs
- Because of the variations in requirements and possible restrictions, REMS can add burden to the healthcare delivery system and may unintentionally create barriers to patient access to the drug

REMS for extended-release and long-acting opioid analgesic products

- On February 6, 2009, FDA notified the application holders of ER/LA opioid analgesics that a REMS was required for their products to ensure that the benefits of those products continued to outweigh their risks.
- In April 2011, FDA officially notified the sponsors of the required components of the REMS after considering the extensive stakeholder feedback, the scope of the REMS, the impact on the health care delivery system and patient access
- On July 9, 2012, FDA approved the shared system ER/LA Opioid Analgesics REMS
  - The primary component was an education program targeted to the prescribers of these products. The education was focused primarily on the risks and safe use of these products.
  - The education was developed by accredited independent CME providers based upon a blueprint developed by the FDA
  - The REMS also included a patient counseling document and product-specific MG as well the requirement for the RPC to assess the impact of the REMS

Public discussion of the ER/LA Opioid Analgesics REMS

- The first full assessment (36-month) of the REMS was the subject of a joint meeting of the Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products Advisory Committees to obtain input on whether:
  - the REMS is meeting its goals
  - there are alternative methodologies for evaluating the program
  - the FDA educational blueprint should be revised and/or expanded;
  - 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 for modifying the REMS

- The REMS should be expanded to include the immediate-release opioid analgesics
- The focus of the education should be expanded to include pain management and risk/benefit of different treatments
- The training should be mandatory for prescribers; most preferred this be implemented either through DEA registration or state licensure
- Training should be expanded to entire health care team, not only prescribers

Advisory Committee recommendations on evaluating the impact of the OA REMS

Assessments could be improved

- Regarding surveys:
  - a better sampling approach is needed
  - surveys that are conducted for evaluation purposes should be shortened
  - sample sizes should be larger and more generalizable
- Changing the level of opioid analgesic prescribing is not helpful without some evaluation of whether the prescribing is appropriate or inappropriate.
  - The committee struggled with how to define appropriate of prescribing
- The committee suggested that there be drug utilization and patient outcomes data tied to the educational program to see how the REMS directly affects physician and patient behavior, and pre vs. post comparisons on those changes in behavior.

The Opioid Analgesics REMS was approved in September 2018

- Includes all IR, ER, and LA opioid analgesics
- The primary component of the OA REMS is education that is targeted to prescribers, pharmacists, nurses and other providers involved in treatment and monitoring of patients with pain
- Manufacturers are required to make education available. They are meeting this obligation by providing unrestricted grants to CE providers to develop content based on an expanded FDA Blueprint (CE training was first available March 1, 2019). The content is completely independent of the RPC

The education under the modified Opioid Analgesics REMS remains voluntary and is not required in order to prescribe or dispense the drug

Patient materials

- Product-specific Medication Guides
- Patient Counseling Document

Opioid Analgesic REMS **Patient Counseling Guide**

What You Need to Know About Opioid Pain Medicines

This guide is for you! Keep this guide and the Medication Guide that comes with your medicine so you can better understand what you need to know about your opioid pain medicine. Go over this information with your healthcare provider. Then, ask your healthcare provider about anything that you do not understand.

What are opioids?

Opioids are strong prescription medicines that are used to manage severe pain.

What are the serious risks of using opioids?

- Opioids have serious risks of addiction and overdose.
- **Too much opioid medicine in your body can cause your breathing to stop – which could lead to death.** This risk is greater for people taking other medicines that make you feel sleepy or people with sleep apnea.
- **Addiction** is when you crave drugs (like opioid pain medicines) because they make you feel good in some way. You keep taking the drug even though you know it is not a good idea and bad things are happening to you. Addiction is a brain disease that may require ongoing treatment.
- Take your opioid medicine exactly as prescribed.
- Do not cut, break, chew, crush, or dissolve your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- When your healthcare provider gives you the prescription, ask:
  - How long should I take it?
  - What should I do if I need to taper off the opioid medicine (slowly take less medicine)?
- Call your healthcare provider if the opioid medicine is not controlling your pain. Do not increase the dose on your own.
- Do not share or give your opioid medicine to anyone else. Your healthcare provider selected this opioid and the dose just for you. A dose that is okay for you could cause an overdose and death for someone else. Also, it is against the law.
- Store your opioid medicine in a safe place

Goal of the OA REMS

The goal of the Opioid Analgesic REMS is to educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain. The education provided through the REMS program is based on the Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint"). Through better education, the healthcare team will have an improved understanding of how to manage pain and the role of opioid analgesics along with nonpharmacologic and non-opioid analgesics in pain management. The education will also provide information about the risks of opioids and use of other therapies which is intended ***to assist healthcare providers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.***

The REMS will accomplish this goal by:

- **Ensuring that training based on the FDA Blueprint is effective** in educating prescribers and other healthcare providers involved in the treatment and monitoring of patients in pain (including pharmacists and nurses) about recommended pain management practices and appropriate use of opioid analgesics.
- **Informing patients about their roles and responsibilities regarding their pain treatment plan**, including the risks of opioid analgesics and how to use and store them safely, as outlined in the Medication Guides and Patient Counseling Guide for opioid analgesics.

REMS Assessments

REMS authorities to require assessments

- When the REMS authorities were put into place, FDA for the first time could require sponsors to conduct an assessment of their risk mitigation strategy.
- The statute under Section 505-1(g)(3) of the FDCA specifies that a REMS assessment shall include an assessment of the extent to which the REMS is meeting the goal(s), or whether 1 or more such goals or such elements should be modified.
- The statute does not specifically describe how a sponsor should conduct an assessment.

Recent criticism of FDA's oversight of REMS assessments

- REMS assessments do not always include the information needed or high quality data necessary to determine if REMS is meeting its goals
- FDA's review of REMS assessments and actions on REMS assessment findings are not timely
- FDA has abandoned its effort to require evaluation of the OA REMS CE impact on prescribing behaviors and patient outcomes

Focus greater efforts on assessment planning

- Develop and incorporate REMS assessment planning into the design of the REMS by directing Sponsors to:
  - Link the design (input) with the assessments (output) and ensure sufficient and appropriate data collection
  - Identify key metrics and thresholds for program success
  - Ensure timely REMS methodology submissions that include sufficient and appropriate data collection and analysis

Risk Minimization Assessment Logic Model

EVIDENCE & UNCERTAINTIES

Characterization of RISK:
- Mechanism of action /preclinical evidence
- Clinical development experience
- Labeled indication and patient population
- Post-marketing real-world evidence

SITUATION

RISK ASSESSMENT

CARE GAP ASSESSMENT

PRIORITIES

REMS
Public Health
Prevention
GOALS

☐ Primary (prevent)
☐ Secondary (screen)
☐ Tertiary (manage)
☐ Informed B-R decision-making

INPUTS
REMS Objectives and Strategies

To directly affect Knowledge-Skills:
□ Medication Guide (patient)
□ Communication Plan (healthcare provider)
□ Prescriber certification and/or training
□ Pharmacy certification

To directly affect Safe Use Behavior:
□ Healthcare setting restrictions
□ Evidence of safe-use conditions before dispensing
□ Required monitoring

To inform RISK MITIGATION actions:
□ Patient registry

OUTPUTS
Implementation Activities

- QA/QC measures (e.g., media plan, training fidelity and outcomes)
- QA/QC measures (e.g., implementation system policies and procedures)
- QA/QC measures (e.g., registry protocol and enrollment processes and procedures)

PERFORMANCE OUTCOMES
Primary (Key Indicator) | *Secondary (Explanatory)*

Dissemination Science Frameworks
- Knowledge
- Behavioral intent
- Attitudes, beliefs
- External influencers

Implementation Science Frameworks
- Observed behavior
- Knowledge, behavioral intention
- Perceived barriers
- Key design assumptions – met?

Biomedical Science Frameworks
- Case reporting
- Sub-group analysis (patient, provider, clinical setting)

HEALTH IMPACT

Integrated Safety & Benefit-Risk Profile

Good pharmacovigilance practices (e.g., case study, case series, epidemiology, clinical)

Observed vs. Expected (?)

Quality Process Improvement Frameworks
Failure Mode & Effects Analysis (FMEA)

Risk Management CARE GAP IDENTIFICATION and DESIGN ASSUMPTIONS:
- Strength of risk management evidence | Effectiveness and translatability of strategies used during clinical development; best practices in clinical care
- Anticipated risk management care gaps | Given healthcare delivery context and expected patient flow, setting and clinical care processes | Key driver diagram
- Baseline risk knowledge, attitudes and beliefs| system, provider, and patients
- Capacity for safe-use behavior | resources, self-efficacy | readiness for change
- Influencing factors | state laws/regulation; insurance policies; guidelines

Real World EXTERNAL FACTORS:
- Evolving health care delivery system
- State laws, regulations, and policies
- Health insurance policies and reimbursement incentives
- Competitive market dynamics

Source: Morrato, Toyserkani, Huynh (*ICPE All Access 2020*)

Components of the Opioid Analgesic REMS Assessment

Metrics on the program outreach and implementation

- Information on the distribution of REMS letters informing HCPs about the availability of the CE
- Status of grants awarded and available CE activities, composition of grant review committee
- REMS CE learner metrics
- Independent audits of CE

12 Grants awarded that include nearly 100 CE activities with a variety of formats

- **Didactic** – follows a consistent scientific approach or educational style
- **Case-based** – first person account of an individualized evaluation, assessment, diagnosis and treatment is presented
- **Multimedia** – education may include film, internet, didactic and other modalities
- **Interactive** – hands-on, real-world approach that actively engages students
- **Adaptive** – an educational approach that uses computer algorithms to orchestrate the interaction with the learner and deliver customized resources and learning activities to meet the unique needs of the learner

REMS CE Learner Metrics: Completers*

CE Completers during reporting period (16 May 2019 – 15 May 2020)	
Total completers	100,778
Completers with prescribing status	70,480
Completers with license to prescribe controlled substances	59,635

*Completer: an individual that has completed all components of an educational activity and meets the CE provider's criteria for passing

REMS CE Learner Metrics: Other characteristics

CE Completers during reporting period (16 May 2019 – 15 May 2020) N=100,778	
Physicians	43,289 (43%)
Advanced Practice Nurse	19,116 (19%)
Pharmacist	11,564 (11.5%)
Nurse	8584 (8.5%)
Physician Assistant	8188 (8.1%)
Dentist	3893 (3.9%)
Podiatrist/Optometrist/Psychologist	433 (0.4%)/192 (0.2%)/61 (0.1%)
Other	5458 (5.4%)

Evaluation of health care provider knowledge

- Pre- and post-CE activity testing
- Long-term follow-up evaluation of participants to assess retention of knowledge

These evaluations inform Objective 1 - Ensuring that training based on the FDA Blueprint is effective in educating prescribers and other healthcare providers involved in the treatment and monitoring of patients in pain (including pharmacists and nurses) about recommended pain management practices and appropriate use of opioid analgesics

Evaluation of patient knowledge and experiences

- Evaluation of patient understanding (knowledge surveys)
- Evaluation on patient experiences around pain management (focus groups)

These evaluations inform Objective 2 - Informing patients about their roles and responsibilities regarding their pain treatment plan, risks, and safe use of opioid analgesics.

Contextual information

- Landscape analysis
  - An evaluation of concurrent educational interventions (states and health system requirements)
  - Summary of major legislative and policy changes
- National data on opioid misuse, abuse, overdose, addiction, and death
  - Mortality data, poison center call data, emergency department visits, national survey data
- National drug utilization trends/patterns
  - Opioid analgesics by drug, prescriber specialty, concomitant benzodiazepines and other CNS depressants

While these evaluations do not directly inform the goal or objectives of the REMS, the data provide contextual information.

Prescriber behavior and patient outcomes

The approval letter specified that the RPC should:

- Use an appropriate control group (i.e., providers who have not completed REMS-compliant CE) to control for confounding to allow for an assessment of whether any observed changes in **prescriber behaviors or patient outcomes** can be attributed to the CE
- Develop and use metrics that assess prescriber behaviors and patient outcomes relating to **key messages in the Blueprint**
- Also include evaluation of potential **unintended adverse patient outcomes** resulting from changes in prescribing practices

These metrics inform the aspirational goals/intent of education and will be the focus of our discussion today

Morning presentations

Blueprint for Heath Care Providers Involved in the Treatment and Monitoring of Patients with Pain: An Overview	LCDR Mark Liberatore, PharmD, RAC Deputy Director for Safety, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience (ON), Office of New Drugs (OND), CDER, FDA
Safer/Competent Opioid Prescribing Education (SCOPE of Pain): Putting the Blueprint into Action	Julie L. White, MS Director, Continuing Medical Education Boston University School of Medicine
Considerations for studying the impact of the OA REMS on practice behaviors and patient outcomes	Jana McAninch, MD, MPH, MS Senior Medical Epidemiologist Division of Epidemiology, OSE, CDER
A Role of Large Data Sources in Assessing Efforts to Improve Opioid Prescribing	Alec Walker, MD, DrPH Principal World Health Information Science Consultants
Developing and Implementing EHR-based Quality Improvement Opioid Measures	Jan Losby, PhD, MSW Branch Chief, Health Systems and Research Branch, Division of Overdose Prevention, Centers for Disease Control (CDC)
Rethinking study designs to quantify REMS effectiveness	G. Caleb Alexander, MD Professor of Epidemiology and Medicine Johns Hopkins Bloomberg School of Public Health
Opioid Analgesic REMS Assessment plan: Additional indicators of success	Doris Auth, PharmD Deputy Division Director (Acting) Division of Risk Management, OSE, CDER
Can We Improve Physician Performance and Patient Health Outcomes Through CME/CPD?	Ronald M. Cervero, PhD Professor and Deputy Director Center for Health Professions Education Uniformed Services University of the Health Sciences

Afternoon agenda

Topic 1 Panel discussion: **Measurable outcomes to evaluate the effectiveness of Opioid Analgesic REMS training**	Moderators: Judy Staffa and Jana McAninch
Topic 2 Panel Discussion: **Feasibility of studying the impact of the OA REMS education on prescriber behavior and patient outcomes**	Moderators: Judy Staffa and Jana McAninch
Topic 3 Panel Discussion: **Alternative approaches to broadly evaluate the impact of CE on prescriber behaviors and patient outcomes**	Moderators: Doris Auth and Claudia Manzo
Pre-registered Public Participation	
High Level Summary	Judy Staffa and Claudia Manzo
Meeting adjourns	


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