



# FDA REMS Program

REMS: Risk Evaluation & Management Strategy

1990s-2011

Pain Management: Prescription Drug Abuse - S. Sandy Sanbar, MD, PhD, JD

This presentation provides an overview of the Food & Drug Administration (FDA) REMS Program for opioid drugs.

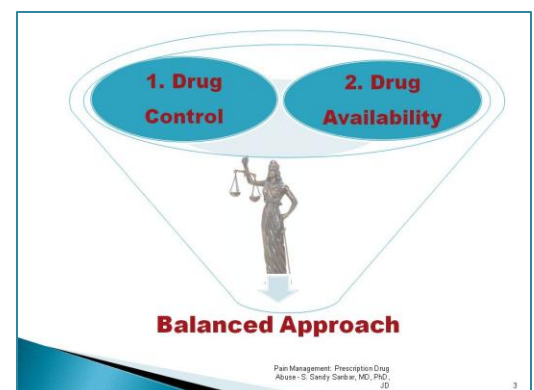
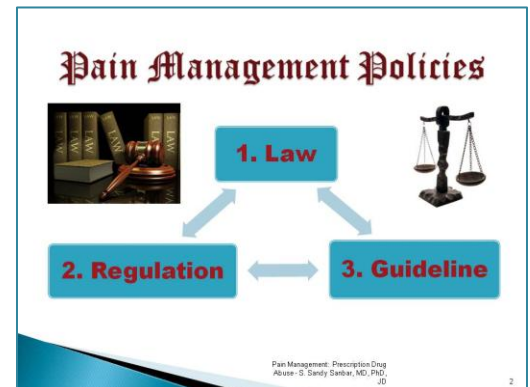
**First**, some background information. Pain management is governed by three types of interrelated policies – namely, Laws, Regulations and Guidelines:

1. **“Law”** – refers to rules of conduct with binding legal force adopted by a legislative or other government body.
2. **“Regulation”** - is issued by an agency of the executive branch of government pursuant to statutory authority and has legal force.
3. **“Guideline”** – has no binding legal force. It is issued by a government agency or a non-governmental organization to express the attitude about, or position on, a particular matter.

**The** purpose of pain management laws, regulations and guidelines is two-fold: Drug Control and Drug Availability.

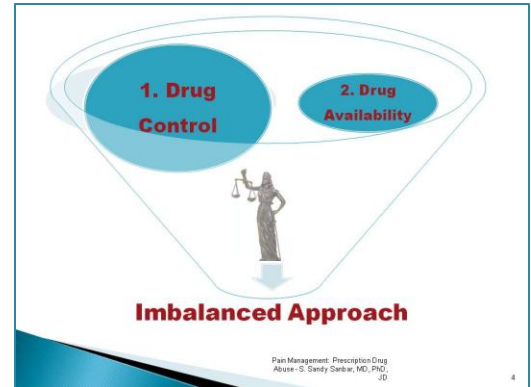
1. **Drug control** by law enforcement is aimed at preventing diversion and abuse of prescription medications.
2. **Drug Availability** to patients, on the other hand, recognizes that many opioids and other controlled substances are necessary for pain relief and that governments must ensure their adequate availability for medical prescribing, dispensing and scientific purposes.

When **both** drug control and drug availability are appropriately recognized in public policy, and *implemented in everyday pain management practice*, this is referred to as the **principle of balance** or in effect a **balanced approach**.



**Review** of Pain management in the U.S. during the past 176 years reveals an imbalanced approach in favor of drug control. In fact, in 1971 the U.S. government declared an all out “War on Drugs” under the Nixon Administration.

Compounding the problem is the fact that the availability of opioid prescription drugs to alleviate the pain and suffering of some patients neither have been appropriately recognized in public policy nor *implemented safely in everyday pain management practice.*



**From the FDA side, REMS programs** are intended to formalize ways to minimize the opioid risks while maintaining access for patients who need opioid medication.

**From the medical side, Good medical practice** requires physicians to maintain the balance of benefits and risks of opioids by:

1. Screening all patients and monitoring them for signs of abuse and addiction;
2. Using an opioid agreement and keeping detailed prescribing records; and
3. Reminding patients/caregivers to take their medication only as prescribed and to protect their prescriptions against accidental use, theft, and misuse.

**Principle of Balance  
Opioid Therapy**

1. FDA REMS for opioid medications.
2. Good medical practice requires:
  - a. Screening & monitoring all patients for signs of abuse and addiction;
  - b. Use opioid agreement;
  - c. Keep detailed prescribing records;
  - d. Educate patients/caregivers:  
Take medication only as prescribed &  
Protect against accidental use, theft,  
and misuse.

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**Law enforcement and specifically the Control of prescription drug abuse** has been of great concern to the U.S. beginning in the 19<sup>th</sup> century. In the early 21<sup>st</sup> century, prescription drug abuse is the Nation’s fastest-growing drug problem. Law enforcement views “Pain Management” with opioids as a public health and public safety crisis because of its potential for diversion, abuse, morbidity, and mortality.

**The Medical Community emphasizes the Principle of Balance.**

The WHO, the APS/AAPM and several other organizations acknowledge

that opioids are an essential treatment option in the management of patients with moderate to severe pain. It is also acknowledged that opioids are associated with significant risks including misuse, abuse, addiction, and overdose.

**Opioid Therapy:  
Law Enforcement  
&  
Principle of Balance**

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**In April 2011**, the Obama Administration unveiled a **Prescription Drug Abuse Prevention Plan** which expands upon the Administration's **National Drug Control Strategy**. The plan comprises four major action areas:

1. **Education** of the public and healthcare providers about the dangers and safe use of prescription drug abuse;
2. Implement prescription drug **monitoring** programs (PDMPs) in every state, share data across states and have healthcare providers use them.
3. Provide law **enforcement** agencies with support and the tools they need to expand their efforts to shut down "pill mills" and to stop "doctor shoppers";
4. Development of consumer-friendly and environmentally-responsible prescription drug **disposal** programs to limit the diversion of drugs.

This presentation addresses primarily the **EDUCATION** component, although the four actions are interrelated.

**In 2007**, the FDA Amendments Act (FDAAA) of 2007 gave the FDA the authority to require Risk Evaluation and Mitigation Strategy (REMS) as part of the ongoing evolution of managing risk. REMS are FDA-mandated requirements to minimize the risks associated with certain medications. An important part of the REMS program is the requirement that drug manufacturers thoroughly educate Health Care providers (HCP) and the Public about their drugs.

1. **The REMS program** focuses on drugs or biologics that have a known or potential safety risk. REMS may be required by the manufacturer prior to approval of a drug or post-approval if new safety information becomes available ,or if it is determined that REMS is necessary to ensure that drug benefits outweigh risks.
2. REMS can be mandated for any medication or class of medication.
3. REMS may include medication guides and Patient Package Insert, communications to healthcare providers, information to patients, elements to assure safe use, and implementation systems to assure safe use.
4. The goal of an opioid REMS is to ensure balance between appropriate access to opioid therapy and risk mitigation .



**FDA** U.S. Food and Drug Administration  
Protecting and Promoting Your Health

FDA Amendments Act (FDAAA) - 2007

**REMS**  
Risk Evaluation & Mitigation Strategy  
[OpioidREMS@fda.hhs.gov](mailto:OpioidREMS@fda.hhs.gov)

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**REMS program**

1. Requires manufacturers to submit REMS with drugs or biologics that have a known or potential safety risk.
2. May include any medication or class of medication
3. May include medication guides, communications to healthcare providers, elements to assure safe use, implementation systems to assure safe use
4. Goal of opioid REMS

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**The following** is a timetable of Opioid Risk Management Plans:

1. **Early 1990s:** Risk Management Plans (RMPs)
2. **2000s:** Risk Minimization Action Plans (RiskMAPs)
3. **2007:** Via the FDA Amendments Act of 2007 (FDAAA), Congress gives FDA the authority to require a REMS when FDA determines a REMS is necessary to ensure the benefits of a drug outweigh the risks.  
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm187975.htm> )
4. **February 2009:** FDA sends letters to manufacturers of certain opioids requiring REMS.  
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm187975.htm>
5. **March 2009:** FDA holds an industry meeting on REMS for certain opioid drugs.<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163660.htm>.
6. **April 2009:** FDA opens a public docket to receive comments on relevant issues (open until end June 2009). <http://edocket.access.gpo.gov/2010/pdf/2010-8831.pdf>.
7. **May 2009:** May 4-5 Stakeholders meet with FDA on opioids and REMS; May 27-28 Public meeting on REMS for certain opioids.  
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.
8. **December 2009:** FDA/industry public meeting on REMS for certain opioids.
9. **May 2010:** FDA re-opens the public docket through October 19, 2010
10. **July 2010:** FDA reveals a proposed REMS for long-acting and extended-release opioids
11. **July 2010:** An FDA advisory committee voted 25-10 to reject the long-acting opioid REMS proposed by the FDA.

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>

<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm214816.htm>

<http://www.fdanews.com/newsletter/article?articleId=128946&issueId=13895>

### Opioid REMS Timetable

- 1990s: Risk Management Plans (RMP)
- 2000s: Risk Minimization Action Plans (RiskMAP)
- 2007: FDA Amendments Act (FDAAA) – REMS
- Feb 09: FDA letters to manufacturers.
- Mar 09: FDA industry meeting on REMS.
- Apr 09: Public docket for comments.
- May 09: Two meetings – Stakeholders; Public
- Dec 09: FDA/industry public meeting.
- May 10: FDA re-opens the public docket 5 mos.
- July 10: FDA REMS for opioids rejected by A.C.
- Oct 10: FDA REMS meeting w/stakeholders.

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**Certain opioid analgesics will be required to have REMS.**

All extended-release oral opioid analgesics:

1. Hydromorphone
2. Morphine
3. Oxycodone
4. Oxymorphone

Methadone and Transdermal fentanyl

**By the end of 2008** there was **one** approved opioid REMS for Nucynta (tapentadol) which is in a group of drugs called narcotic pain relievers. It is similar to morphine and is used to treat moderate to severe pain. (Registered trademark of Ortho-McNeil-Janssen Pharmaceuticals).

**Three** REMS were approved in 2009 for **DARVON** (Xanodyne Pharmaceuticals), **EMBEDA**® (morphine sulfate and naltrexone hydrochloride), and **Onsolis** (Fentanyl Buccal, Transmucosal , Meda Pharmaceuticals Inc. ) bringing the total at the end of 2009 to **four**.

By 2010, a total of seven drugs required REMS, and in early 2011, the number reached 12, as noted in the slide.

**The Opioids** used for moderate-to-severe pain can be classified into various categories:

1. Long-acting opioids (LAOs) including extended-release opioids  
Longer onset and longer duration of analgesia
2. Short-acting opioids (SAOs) -
  - a. Traditional short-acting opioids have an onset of 30–45 minutes and a shorter duration of analgesia
  - b. Rapid-onset opioids (ROOs) have an onset of 15 minutes or less and a shorter duration of analgesia

The FDA discussion has centered on the long-acting opioids class-wide REMS. The REMS requirements for ROOs are under review. The FDA has not required a class-wide REMS for other Short-acting opioids.

**Opioid Analgesics Required to Have a REMS**

- All extended-release oral opioids:
  1. Hydromorphone
  2. Morphine
  3. Oxycodone
  4. Oxymorphone
- Methadone
- Transdermal fentanyl

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**REMS Approved**

- **2008:** Nucynta
- **2009:** Darvon, Embeda & Onsolis
- **2010:** Exalgo, morphine sulfate, & OxyContin
- **2011:**

Avinza	Duragesic
Butrans	Dolophine
Embeda	Exalgo
Kadian Capsules	MS Contin
Opana ER	Oramorph
OxyContin	Palladone

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**Opioid Classifications**

- ▶ Moderate-to-severe pain categories:
  1. Long-acting opioids (LAOs)
  2. Short-acting opioids (SAOs)
    - a. Traditional short-acting opioids
    - b. Rapid-onset opioids (ROOs)
- ▶ FDA – LAO require class-wide REMS
- ▶ REMS for ROOs are under review
- ▶ No class-wide REMS for other SAOs

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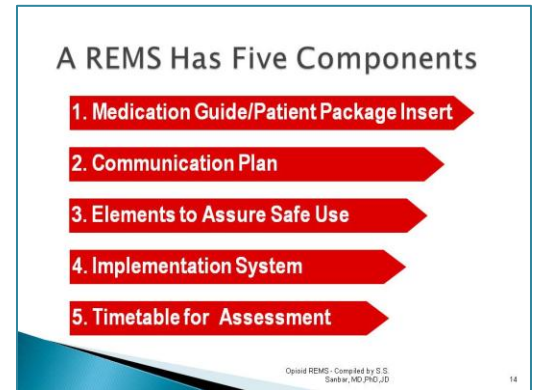
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**Source:** Draft Guidance. *Guidance for Industry: Format and content of proposed Risk Evaluation and Mitigation Strategies (REMS), REMS assessments, and proposed REMS modifications.* US Department of Health and Human Services. Food and Drug Administration, September 2009.

There are five different components for a drug REMS.

1. **Medication Guide/PPI** (patient package insert) - Educational tools provided to each patient when the drug is prescribed / dispensed.
2. **Communication Plan** – For example, letters to healthcare providers, communications to professional societies, professional education, etc.
3. **Elements to Assure Safe Use (ETASU)** - Special requirements or restrictions to optimize safe use of products.
4. **Implementation System** - System to monitor, evaluate, and improve elements to assure safe use.
5. **Timetable for Assessment** - Minimum FDA requirement 18 months, 3 years, and 7 years after REMS approval. This element is the only compulsory element for all REMS programs.

An individual program does not have to include all five components. Of the five components, the two that are most relevant to prescribers are the Medication Guide/PPI, and Elements to Assure Safe Use (ETASU).



**Components of Existing REMS**

Examples	Medication Guide	Communication Plan	Elements to Assure Safe Use	Implementation System	Timetable for Assessment	Products (n)
Parvon, Nucynta, Morphine sulfate	●	●	●	●	●	89
Botox, Embeda, Simponi	●	●	●	●	●	29
Exalgo, OxyContin	●	●	●	●	●	4
Letairis, Promacta, Tracleer	●	●	●	●	●	2
Entereg, Sucraid	●	●	●	●	●	4
NPlate, Onsolis, Sabril	●	●	●	●	●	6

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**ETASU** may be required if the drug is associated with a serious adverse event and the medication guide, Patient Package Insert, or communication plan plus assessment are not sufficient to mitigate these risks

ETASU may require any of the following:

1. Training / certification of prescribers;
2. Training / certification of pharmacists / pharmacies;
3. Restrictions on where the drug is dispensed;
4. Evidence of patient safe use conditions;
5. Patient monitoring;
6. Enrollment of patients in a registry.



## Communication

The American Society for Automation in Pharmacy (ASAP) has announced a new version of its widely used standard for prescription-monitoring programs (PMPs). This new Standard for Real-Time “Safety Adjudication” for REMS ETASU Programs based on the current American Society for Automation in Pharmacy (ASAP) Prescription Monitoring Program (PMP) transaction that is widely used today. The latest version follows the design and syntax of the 2005 ASAP standard, but it has been enhanced to allow for more precise reporting of controlled substances and other drugs required by state reporting programs.

This new communication standard is designed to support the various Elements to Assure Safe Use (ETASU) requirements of a REMS program. It is designed to minimize software development time and time to market.

**The following is an example** of how to look up Online a REMS for an opioid, in this case OxyContin.

First, Google “Oxycontin REMS” and login to obtain the Home page.

There are links on the **Home Page**:

1. **For Patients & Caregivers**
2. **For Healthcare Professionals**

Click on “For Health Professionals” and you will find three links which you should open and read:

1. **Dear Healthcare Professional Letter**
2. **Healthcare Provider Training Guide**
3. **Education Confirmation Form**

You will also find the **IMPORTANT SAFETY INFORMATION WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE**

And, Please click [here for Full Prescribing Information](#).

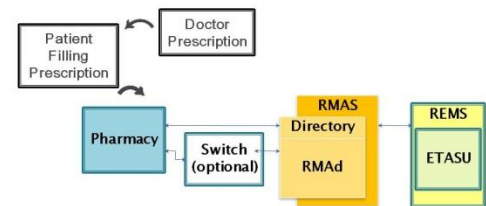
### New ASAP REMS ETASU Standard

- ▶ Standard for Real-Time “Safety Adjudication” for REMS ETASU Programs
- ▶ ASAP Prescription Monitoring Program (PMP) transaction
  - Support various Elements to Assure Safe Use (ETASU) requirements of a REMS program.
- ▶ Minimize software development time and time to market

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### Outpatient Pharmacy Prescription Verification



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e.g. **OXYCONTIN<sup>®</sup>**  
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

*Risk Evaluation and Mitigation Strategy*

Website:

<http://www.oxycontinrems.com/>

Home Page

1. **For Patients & Caregivers**
2. **For Healthcare Professionals**

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**OxyContin<sup>®</sup> REMS Website**  
Information on proper use and potential risks of Oxycontin<sup>®</sup>

**HEALTHCARE PROFESSIONALS**

#### For Healthcare Professionals

1. Dear Healthcare Professional Letter
2. Healthcare Provider Training Guide
3. Education Confirmation Form
4. **IMPORTANT SAFETY INFORMATION WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE**
5. Please click [here for Full Prescribing Information](#).

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## HEALTHCARE PROFESSIONAL LETTER

By clicking on the **“Dear Healthcare Professional Letter”** from the Manufacturer, the letter re-iterates the purpose of the REMS, the goals to EDUCATE both the physicians and patients about the benefits and risks of the drug, prescribing and dispensing information, misuse and abuse, patient counseling and the four contents included in the packet.

## TRAINING PROGRAMS

There are two types training programs, one on line and the second by print.

Physicians who prescribe opioids are required to “Complete Training Program” for each drug prescribed that has approved REMS.

In addition, the physician is required to complete the “Education Confirmation Form”, which comprises exam questions.

## HOW TO GET READY FOR REMS

1. Coordinate the office, clinic and pharmacy policies by reviewing your current standard operating procedures and staff roles to prepare for more interaction with staff, patients, and pharmacists and for potential new documentation requirements with REMS.
2. Ensure that you understand the federal and state regulations on prescribing opioids REMS are an addition to, and not a replacement for, federal and state regulations.
3. Visit <http://www.nascsa.org/stateProfiles.htm> (National Association for State Controlled Substances Authority) to find links to access a state’s profile. The profile contains information and additional links to the state’s controlled substance regulatory functions.
4. Visit <http://www.justice.gov/dea/index.htm> (DEA website) for controlled substance policies

**OxyContin**  
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS  
*Risk Evaluation and Mitigation Strategy*

Dear Healthcare Professional Letter

1. REMS Purpose: Educate Prescribers
2. Two Goals: Inform Patients & Healthcare Professionals
3. *Prescribing and Dispensing*
4. *Misuse and Abuse*
5. *Patient Counseling*
6. Four items included in the packet

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OxyContin® educational training program documents

**Take Training Now**

Complete Training Program and Education Confirmation Form Online

**Download / Print Training**

Healthcare Provider Training Guide

Education Confirmation Form

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### Get Ready For REMS

- ▶ Opioid prescribing patterns
- ▶ Talk to colleagues and peers
- ▶ Supplied written materials for opioids
  - Medication Guide
  - Patient Prescribing Information

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### How To Get Ready For REMS

- ▶ Review SOP and Coordinate the office/clinic/pharmacy
- ▶ Understand federal and state regulations on prescribing opioids
  - REMS are an addition to federal and state regulations

<http://www.nascsa.org/stateProfiles.htm>

<http://www.justice.gov/dea/index.htm>

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## **PATIENT COMMUNICATION**

Enhance Communication with patients. Explain that REMS are coming and that there may be new requirements with their opioid medications

### **Six Steps to Zero**

(Source: <http://www.zerodeaths.org/staying-safe/six-steps-to-zero/> )

1. **Never take a prescription painkiller unless it is prescribed to you.**

Everyone responds differently to pain medications. What is safe for one person may not be safe for another.

2. **Do not take pain medicine with alcohol.**

Never mix the two; it is a dangerous combination that can be deadly. Alcohol increases the toxicity of pain medication.

3. **Do not take more doses than prescribed.**

Even after the effects of pain medicine seem to have worn off, it is still depressing the respiratory system. The body must develop a tolerance to the respiratory depressant effects before the dose can be increased.

4. **Use of other sedative or anti-anxiety medications can be dangerous.**

Combining pain medicines with other sedative drugs, such as valium, can increase the toxicity of the pain medication. Only take other medications, if directed by the prescribing doctor.

5. **Avoid using prescription painkillers to facilitate sleep.**

Prescription pain medications can suppress respiration during sleep. Speak to your physician about safe methods to manage pain during sleep.

6. **Lock up prescription painkillers.**

If consumed by children or other family members, or stolen and sold on the street, prescription pain medicine can kill.

#### **PATIENTS: When using opioids:**

1. Never take a prescription painkiller unless it is prescribed to you;
2. Do not take pain medicine with alcohol;
3. Do not take more doses than prescribed;
4. Use of other sedative or anti-anxiety medications can be dangerous;
5. Avoid using prescription painkillers to facilitate sleep;
6. Lock up prescription painkillers.

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## **SUMMARY**

FDA has proposed a class-wide REMS program for long-acting opioids. There is not yet a class-wide REMS for short acting opioids, including rapid onset opioids. In the interim, you will have to work with an increasing number of unique opioid REMS programs.

Technology needs to be further developed to aid HCP's in managing the various REMS programs and complexities. ASAP has created a new communication standard that allows a Pharmacy Management System (PMS) to send required safety data to a Risk Evaluation and Mitigation Strategy (REMS) database.

#### **In Sum, We Know in 2011**

- ▶ Class-wide REMS for long-acting opioids
- ▶ No class-wide REMS for short acting opioids
- ▶ Unique opioid REMS programs
- ▶ Technology to aid HCP's
- ▶ New communication standard
- ▶ Pharmacy Management System (PMS) to REMS database
- ▶ Need to get ready for REMS

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