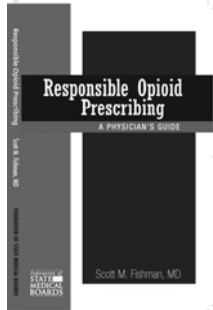


REMS



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Disclosure



- » I am not a lawyer or regulator and I do not offer legal or regulatory advice
- » Information presented here is from the perspective of a concerned physician
- » I collaborate with almost every pain management related pharmaceutical and medical device company
 - ~ through CME speaking (NO Speakers Bureaus / Ad Boards)
 - ~ Stay clean through diversity
- » No other conflicts of interest

Food and Drug Administration Amendments Act (FDAAA) of 2007

- Signed into law September 27, 2007
 - » Primary goal to enhance medical product safety
 - » Represents many significant additions to FDA authority -- 200 specific provisions
- Risk Evaluation and Mitigation Strategies (REMS)
 - » FDAAA authorizes FDA to require a "REMS" for new drug applications and drugs already approved if the Agency determines it's necessary to ensure that the benefits of the drug outweigh the risks
 - ~ Currently, REMS are in place for drugs such as isotretinoin and thalidomide, with mandatory patient counseling, physician/patient treating agreements and national registries for prescribers, dispensers and patients

REMS Risk Evaluation & Mitigation Systems 25 Drugs & Biologics



FDA News

FOR IMMEDIATE RELEASE
 March 27, 2008

Media Inquiries:
 Chris D'Amico (301) 795-8747
 Consumer Inquiries:
 800-FDA-1088

FDA Identifies First Steps in Requirements for Safety Plans for Certain Drugs and Biologics

The U.S. Food and Drug Administration has identified 25 drugs and biologic products that will be required to submit safety plans called Risk Evaluation and Mitigation Strategy (REMS), the FDA said in a Federal Register notice published today.

Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA can require manufacturers to submit a REMS when a drug first comes on the market, or later if FDA becomes aware of new safety data about the drug. The manufacturers of the 25 drugs and biologic products identified in today's notice must submit to the agency a proposed REMS by Sept. 21, 2008.

Certain drugs present a dilemma. They can provide an important benefit to patients, but they can be especially dangerous if not used properly. For example, certain drugs may be safe and effective for patients, but if taken while pregnant can harm the fetus or cause miscarriage. Rather than deny FDA approval of such drugs, the agency has granted approval and required that the manufacturer develop a safety plan, or REMS, to help ensure that health care professionals prescribe the drug correctly and that patients use it safely. While FDA has previously approved some drugs and biologics with these safety plans, the new law makes explicit FDA's authority to require them and contains specific enforcement authority when violations or noncompliance with the plan requirements occur.

"These safety plans allow patients to have continued access to certain medicines for which there are safety concerns that can be managed through appropriate use," said Jane Avineta, associate director for policy, Center for Drug Evaluation and Research, FDA. "The FDA approved the drugs identified today before the new law was passed, and they will now be brought under the new statutory authority to require and enforce REMS."

6 Elements of REMS

March 7, 2008

1. Health care providers who prescribe the drug have particular training, experience, certification
2. Pharmacies, practitioners or health care providers that dispense the drug are specially certified
3. Drug dispensed to patients only in certain health care settings
4. The drug is dispensed with documentation of safe use conditions, such as lab results
5. Each patient taking the drug subject to monitoring
6. Each patient using the drug enrolled in a registry

FDA Release
 September 2009

Draft Guidance

NON-BINDING

90 day Comment
 Period

Guidance for Industry
 Format and Content of
 Proposed Risk Evaluation and
 Mitigation Strategies (REMS),
 REMS Assessments, and
 Proposed REMS Modifications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Director of Drug Information (D-10), Food and Drug Administration, 5630 Fishers Lane, rm. 1063, Rockville, MD 20852. All comments should be identified with the draft number listed in the notice of availability that appears in the Federal Register.

For questions regarding this draft document contact (CBER) Kathleen Ford, 301-793-2988, or (CDER) the Office of Communications, Outreach, and Development (OCOD) at 301-427-1800 or 800-633-6745.

U.S. Department of Health and Human Services
 Food and Drug Administration
 Center for Drug Evaluation and Research (CDER)
 Center for Biologics Evaluation and Research (CBER)

September 2009
 Drug Safety

Elements of Sept. 2008
FDA Draft Guidance Document

- A Medication Guide
- A patient package insert if such insert may help mitigate a serious risk of the drug
- A communication plan to health care providers if the plan may support implementation of an element of the strategy

Elements of Sept. 2008
FDA Draft Guidance Document

- Elements to Assure Safe Use *ETASU*
 - ~ Required if drug shown to be effective, but associated with a serious adverse event
 - » Training, experience, or certification of health care providers who prescribe the drug
 - ~ Periodic recertification or re-enrollment
 - » Certification of pharmacies, practitioners, or health care settings that dispense the drug

Elements of Sept. 2008
FDA Draft Guidance Document

- Elements to Assure Safe Use *ETASU*
 - » Drug be dispensed to patients only in certain health care settings, such as hospitals
 - ~ Ensure drug dispensed only to patients in hospitals that have met certain conditions
 - ~ Ensure drug dispensed only to physicians' offices equipped to treat potential risks associated with the drug following administration of the drug
 - e.g., access to medication and equipment necessary to treat a serious allergic reaction

Elements of Sept. 2008
FDA Draft Guidance Document

- Elements to Assure Safe Use *ETASU*
 - » Drug dispensed only to patients with evidence or other documentation of safe-use conditions, such as laboratory test results
 - » Each patient using the drug be subject to certain monitoring
 - » Each patient using the drug be enrolled in a registry

Onsolis
BioDelivery Sciences International

- Buccal fentanyl
 - » Transmucosal delivery
 - » Soluble film product
- Approved for breakthrough pain in cancer
- Submitted in October 2007
- Approved with a REMS
 - » July 16, 2009

Onsolis
BioDelivery Sciences International

- REMS
 - » "Focus" Implementation programs
 - » Managed by an outsourced vendor for the registration and dispensing of Onsolis
 - » Patients, health care providers, pharmacists and pharmacies must register and adhere to certain requirements of program before Onsolis can be dispensed

Onsolis
BioDelivery Sciences International

- Healthcare providers who prescribe ONSOLIS™ are specially certified
- Each certified prescriber is educated and enrolled in the FOCUS™ Program
- Each certified prescriber vows to the following:

Onsolis REMS
Specific Provisions

- I have reviewed the Prescribing Information for ONSOLIS™ and the educational materials for the FOCUS™ Program. I have completed the Prescriber Knowledge Assessment, and I understand the risks and benefits of chronic opioid therapy
- I understand that ONSOLIS™ can be abused and this should be considered when prescribing or dispensing ONSOLIS™ in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional

Onsolis REMS
Specific Provisions

- I understand that ONSOLIS™ is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain
- I understand that ONSOLIS™ is not bioequivalent with any other oral transmucosal fentanyl citrate product and therefore should not be converted from other oral transmucosal fentanyl citrate products on a microgram-per-microgram basis.

Onsolis REMS
Specific Provisions

- I will provide a completed, signed copy of the patient enrollment form for each patient to the FOCUS™ Program for ONSOLIS™
- I will promptly respond to requests for additional information from the FOCUS™ Program

Onsolis REMS
Specific Provisions

- I will prescribe ONSOLIS™ to patients only after obtaining a signed FOCUS™ Program for ONSOLIS™ Patient Enrollment Form for each patient that documents the following safe use conditions:

Onsolis REMS
Specific Provisions

- Conditions:
 - » Patients using ATC opioid analgesia for at least 1 week
 - » Patients are opioid tolerant:
 - ~ patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer;
 - » Patients or legally authorized representatives counseled about risks and benefits and appropriate use of ONSOLIS™, and risk of overdose due to giving ONSOLIS™ to someone for whom it has not been prescribed
 - » Patients or legally authorized representatives have been provided and have reviewed the education materials

Onsolis REMS Specific Provisions

- Biodelivery Science (BSDI) will maintain a database containing a list of all enrolled prescribers and their status to help ensure that ONSOLIS™ is only prescribed by active prescribers
- Prescribers who write a prescription for ONSOLIS™ and have not written a prescription for ONSOLIS™ to any patient, or enrolled/re-enrolled in the FOCUS™ Program, within the last year will receive a telephone call from a FOCUS™ Program professional reminding them of the prescriber responsibilities under the FOCUS™ Program and asking if they have any questions

Onsolis REMS Specific Provisions

- ONSOLIS™ will only be dispensed by particular pharmacies
 - » ONSOLIS™ will not be available in other healthcare settings, such as retail outlet pharmacies or hospitals
- The FOCUS™ Program prescription process:
 - » Prescriber faxes the initial prescription information for ONSOLIS™ to the FOCUS™ Program to start the verification process
 - » Prescriber sends the original, hardcopy prescription for ONSOLIS™ to a FOCUS™ pharmacy via courier using the supplied, pre-paid shipping label/airbill for a FOCUS™ Program courier
 - » Upon receipt of the original, hardcopy prescription, the FOCUS™ pharmacy dispenses ONSOLIS™ and delivers the medication directly to the patient via a secure, traceable courier



Morphine Sulfate and Naltrexone

- Approved August 13, 2009
 - » Management of moderate to severe pain
 - » No Abuse resistant indication
- Interim REMS equivalent to past Risk Minimization Action Plans (RiskMAPs)



- Interim REMS
 - » Medication Guide
 - » Communication Plan
 - ~ Letters emphasizing key safety messages
 - » Elements to Assure Safe Use
 - ~ **Approved without any elements**
 - » Implementation System
 - ~ Not required

Final Classwide REMS

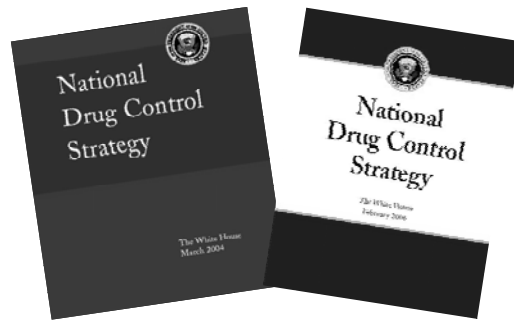
- Ongoing development
 - » No timeline for completion
 - » Numerous public hearings and diverging opinions in testimony
 - » Received unprecedented number of comments in Federal Register from their open docket

What public policy decisions will **FURTHER** the desired goal?

- Develop REMS education programs with extensive expert input
- Implement a national (or coordinated state) Prescription Monitoring Program (PMP)
 - » Point of Care availability for physicians and pharmacists
 - » Prescribers must be able to access PMP data from a confidential site, so that this information can be used as a prophylactic, rather than reactive, tool
 - » Auditing system must be in place as a ready means of attributing REMS effectiveness

THE NATIONAL ALL SCHEDULES
PRESCRIPTION ELECTRONIC
REPORTING ACT OF 2005
(NASPER H.R.3015)

- National Prescription Monitoring Program
 - » Promise of improving pain care
 - ~ Greater oversight of abusible drugs
 - ~ Clinical utility at point of care
 - » Risks associated w/ chilling effects on pain control
 - ~ Clear message to prescribers
 - ~ Confidentiality concerns
 - ~ Variable PMP plans



Prescription Drug Abuse

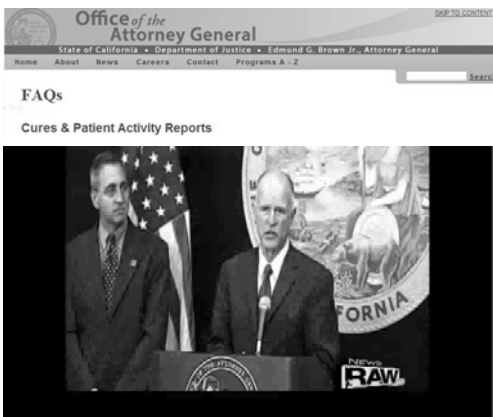
- *“We are now closing this gap in part through the development of something most Americans assume already exists—state-level prescription monitoring programs. PMPs, as they are known, are designed to facilitate the collection, analysis, and reporting of information on the prescribing, dispensing, and use of pharmaceuticals”*

White House Press Release
National Drug Control Strategy, 2004

Prescription Drug Abuse

- *“The effectiveness of PMPs can be seen in a simple statistic: in 2000, the five states with the lowest number of OxyContin prescriptions per capita all had PMPs.”*
- *“According to DEA, the five states with the highest number of prescriptions per capita all lacked them”*

White House Press Release
National Drug Control Strategy, 2004



What public policy decisions will **FURTHER** the desired goal?

- **The REMS should cover the entire class of opioid medications**
 - » Attempt to regulate only a portion of the opioid class of medications will drive prescribers, users, and misusers of these medications to the other, less stringently regulated, but often abused members of the class of medications
 - » Otherwise abuse or misuse will not diminish but will very likely result in decreased access to appropriate therapy for some legitimate patients

What public policy decisions will CONFOUND the desired goal?

- Do not include Patient Registries in the REMS.
 - No evidence exists to suggest that patient registries diminish abuse or misuse
 - Such approaches can stigmatizes patients and imposes significant burdens on all parties, resulting in a chilling effect on prescribing and inadequate pain management
 - Enhancements to the existing and growing state Prescription Monitoring Programs infrastructure would be a better option to consider for achieving the REMS goals

What public policy decisions will CONFOUND the desired goal?

- REMS must protect and not interfere with patient access to important medicines
 - » Stated goal of REMS is similar to the well known policy principal of balance
 - ~ Curb abuse, misuse, and diversion while maintaining appropriate access for legitimate patients to opioid medications that are essential to ease suffering from pain.
 - » Evaluation of the REMS and its impact on these goals will be essential to ensure this balance is maintained

Conclusions

- REMS are still a work in progress
- We are now within a 90 day period for comment to the FDA through the Federal Register
- Several new opioid compounds are on the verge of FDA approval
 - » Most have Abuse-Resistant features
 - » None are asking for Abuse-Resistant Labeling
 - » All will likely get interim REMS until Class-Wide REMS approved
- Stay Tuned

THANK YOU : For Slides: smfishman@ucdavis.edu

