



Risk Management in the United States

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Disclosure Declaration

Disclosure for Erin South. I have no actual or potential conflict of interest in relation to this presentation.

Learning Objectives

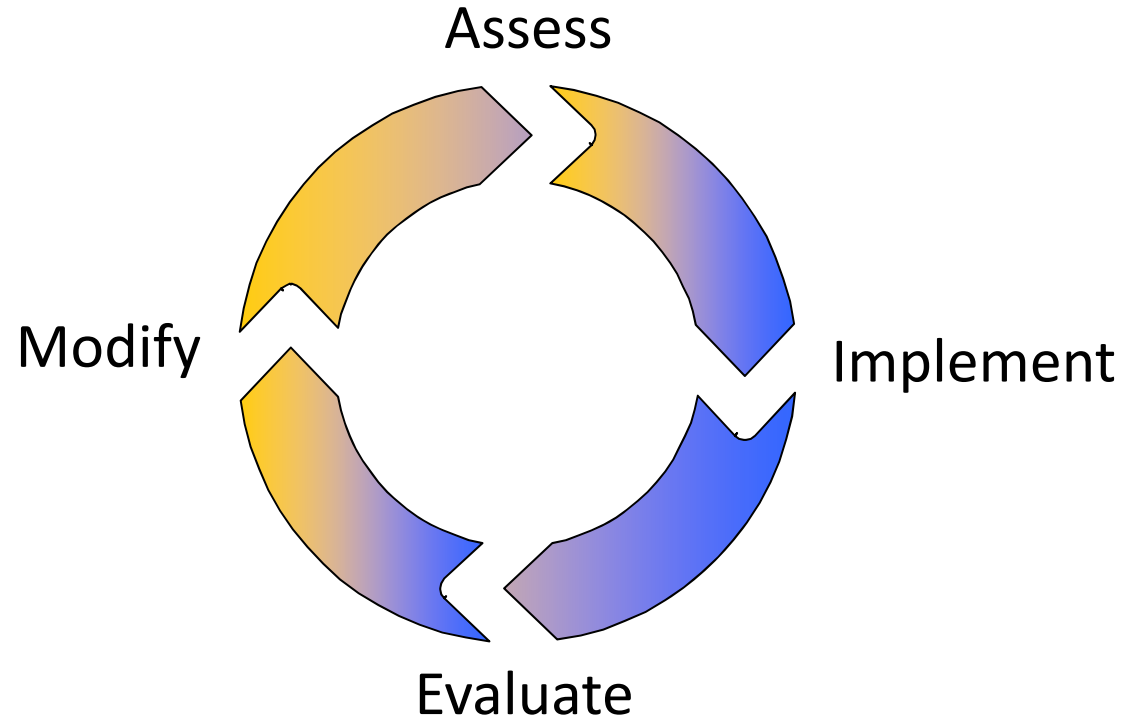
Upon completion of this activity, participants will be able to:

- Describe the history of drug risk management in the U.S. to date
- Describe the factors listed in the statute that should be considered in determining the need for a REMS.
- Describe the elements of a REMS.
- Describe the purpose and minimum requirements for submission of the assessment of a REMS.
- Describe the elements of specific REMS programs that demonstrate consideration of diversity in dispensing.

What is Risk Management?

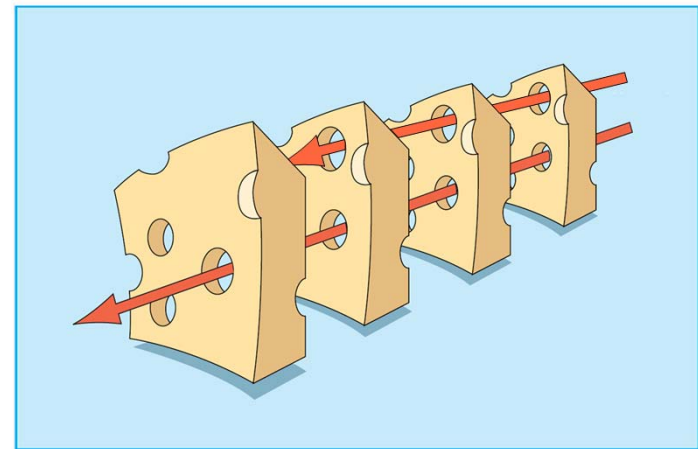
Risk Management Concept

Risk Assessment + Risk Minimization = Risk Management



Risk Mitigation

- Risk mitigation is often accomplished by introduction of a series of steps or processes that lower likelihood of unsafe use
 - May reinforce good clinical practices
 - May introduce new risk mitigation measures
 - May include administrative checks to support risk mitigation efforts
- Each intervention that is part of risk mitigation may introduce some level of burden

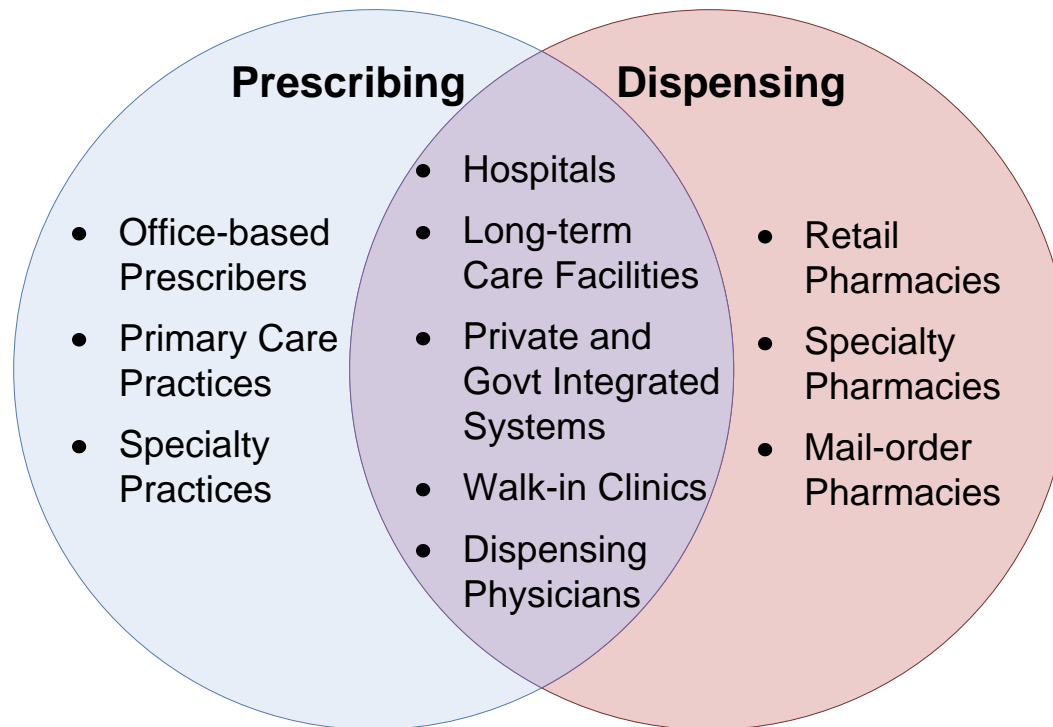


Adapted from: Reason J. Human Error: Models and Management. *British Medical Journal* 2000

Recognize diversity in the healthcare system



- Healthcare system is diverse and processes differ across settings



The foundation of risk management for drugs and therapeutic biologics



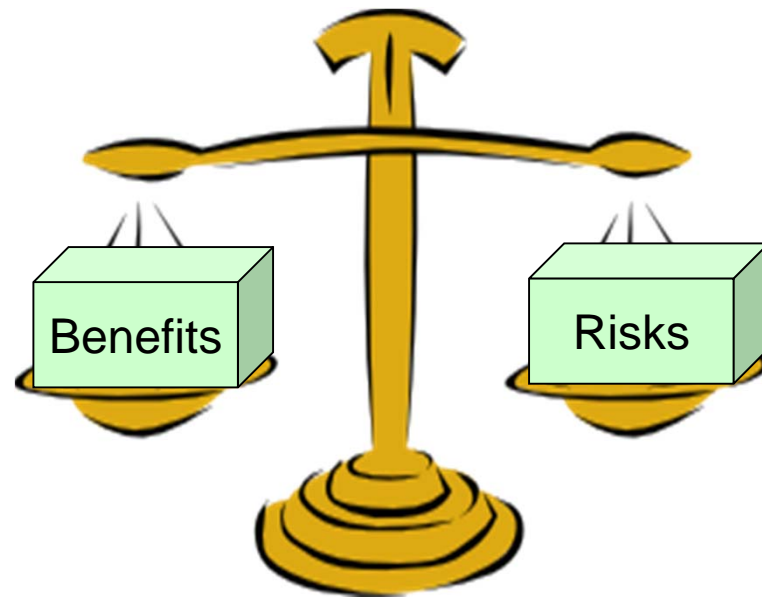
- Product safety issues are typically managed through:
 - Labeling is the cornerstone of risk management and the foundation for the risk management of products
 - Routine reporting requirements allows us to continually assess the benefit risk profile of the product



Why do we need additional risk management tools?



- In a small number of drugs/biologics, additional measures are necessary to mitigate risks and preserve benefits.

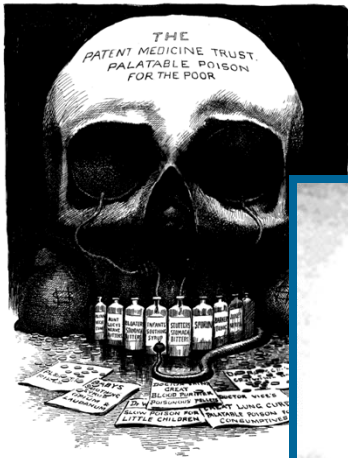


Risk Management for Drugs and Therapeutic Biologics in the U.S.



The Past...

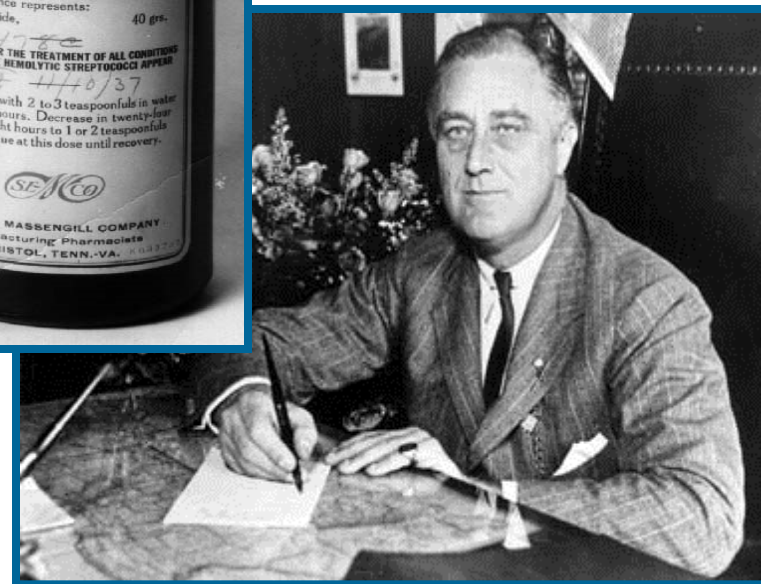
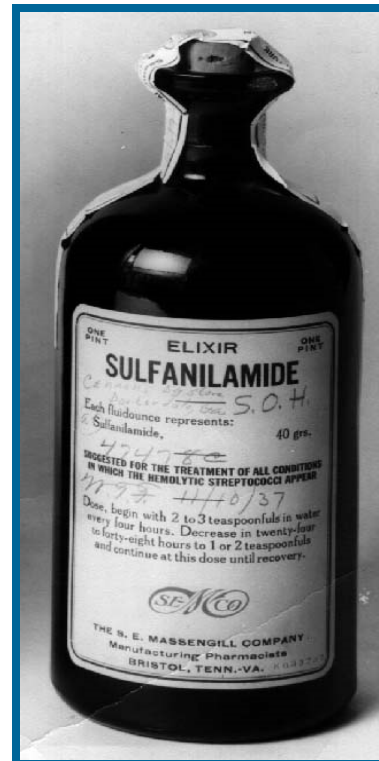
Collier's THE NATIONAL WEEKLY



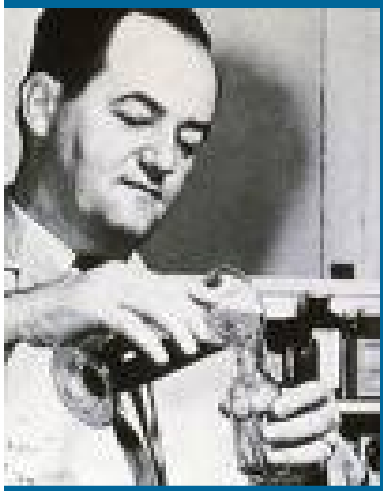
DEATH'S LABORATORY

Patent medicines are poisoning people throughout America today. Babies who cry are fed laudanum drops. Women are led to ingest chemicals for life by reading in the papers about the meaning of life. And boys are misled and contaminated by various criminals who force them to their doom through...

DRAWN BY H. W. KERRY



The Past...



1906: Pure Food and Drug Act

1938:

1951:

1962:

1970:

Food, Drug, and Cosmetic Act
 Prohibited interstate commerce of adulterated or misbranded drugs (identified the US Pharmacopeia and the National Formulary as the official standards for Drugs)

- Required the presence and amount of selected dangerous or addicting substance be labeled

- Enabled the government to take action against illegal products

1970s:

1980-199

Limitations

1998:

- Failed to regulate medical devices and cosmetics and did not provide authority to conduct factory inspections

1998:

1999:

- No ability to control what drugs could be marketed

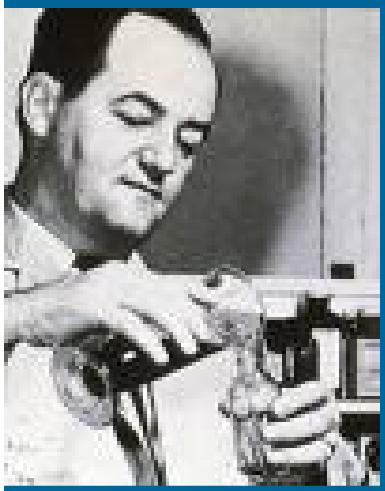


Control

ated

product

The Past...



1906: Pure Food and Drug Act

1938: Food, Drug and Cosmetic Act

1951: Durham-Humphrey Amendment

1962:

1970:

Firms had to **PROVE** to FDA that any new drug was **SAFE** before it could be marketed – the birth of the “new drug application”

1970s:

Invigorated by the 107 deaths caused by the elixir sulfanilamide (containing diethylene glycol (antifreeze)).

1980-1990s:

1998:

Included regulation of cosmetics and devices, authorized factory inspections, and outlawed bogus therapeutic claims

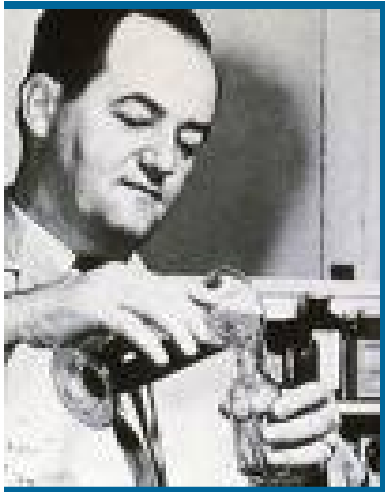
1998:

1999:



FDA publishes *Managing the Risks from Medical Product Use*

The Past...



1906: Pure Food and Drug Act

1938: Food, Drug and Cosmetic Act

1951: Durham-Humphrey Amendment

1962: Kefauver-Harris Amendment

1970: Defines the kinds of drugs that cannot be used safely without medical supervision and restricts their sale to prescription by a licensed practitioner

Control

1970s: Methadone distribution restricted to patients treated for opioid addiction

1980-1990s: FDA develops first risk management programs

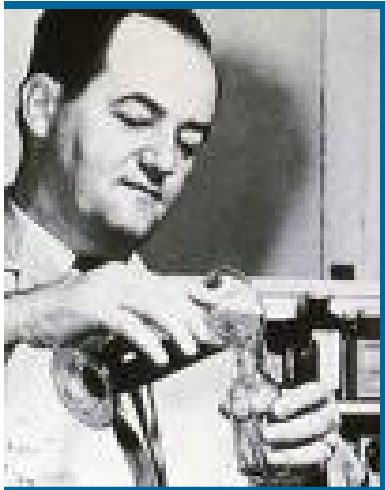
1998: Adverse Event Reporting System (AERS)

1998: Medication Guide regulation (21 CFR 208)

1999: FDA publishes *Managing the Risks from Medical Product Use*



The Past...



1906: Pure Food and Drug Act

1938: Food, Drug and Cosmetic Act

1951: Durham-Humphrey Amendment

1962: Kefauver-Harris Amendment

1970: FDA requires the first patient package insert

Dr. Frances Kelsey - FDA medical officer in charge of thalidomide review and believe the data were incomplete to support the safety of the drug

1970s:

1980-1990s: Manufacturers had to **PROVE** to FDA that their drugs were **EFFECTIVE AND SAFE** before they could go to market

1998:

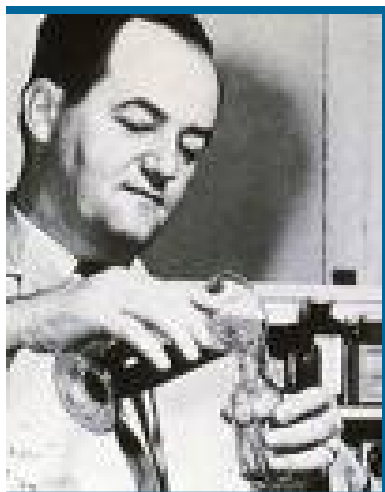
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The Past...



1906: Pure Food and Drug Act

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1951: Durham-Humphrey Amendment

1962: Kefauver-Harris Amendment

1970: FDA requires the first patient package insert
The Comprehensive Drug Abuse Prevention and Control Act



1970s: Methadone distribution restricted to patients treated

1980-1990s: First patient package insert is required for Oral contraceptives, which must contain information for the patient about specific risks and benefits

1998:

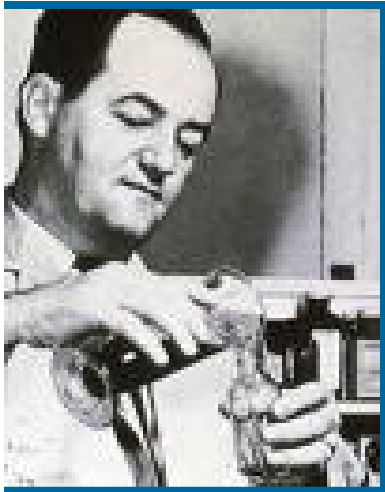
1998: Categorizes drugs based on abuse and addiction potential and medical value

1999:

Use

product

The Past...



- 1906: Pure Food and Drug Act
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1998: Adverse Event Reporting System (AERS)

FDA develops restricted distribution programs

1998:

1999: FDA publishes *Managing the Risks from Medical Product Use*



Early Risk Management Programs (RMP): Accutane[®] (isotretinoin) Pregnancy Prevention Program

- Approved indication (US): severe recalcitrant nodular acne (1982)
 - Pregnancy Category X
- 1988 Dermatologic Advisory Committee meeting
- Pregnancy Prevention Program elements included:
 - Boxed warning
 - Informed Consent for female patients
 - Pregnancy Prevention Program Kit for prescribers
 - Accutane Survey and Prescriber Tracking Survey
 - Educational efforts
 - REMS Approved 10/2010

xx3

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xx3

remove the picture of the pregnancy/women

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Thalomid[®] (thalidomide): S.T.E.P.S. Program



- Approved indications (US)
 - Erythema nodosum leprosum (1998)
 - Multiple myeloma (2006)
- System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)
- Restricted distribution requirements:
 - Enrollment of prescriber, pharmacy, and all patients
 - Pregnancy testing + use of reliable contraception
 - Telephone survey by prescribers and patients
 - Voluntary survey of subset of FCBP
 - REMS Approved 8/2010

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xx1 the picture was used but there were problems with it. Some people thought it was to prevent pregnancy

Considering taking it off.

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xx4 remove

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The Past...

June 2002:

Prescription Drug User Fee Act (PDUFA) III

Feb 2005:

Drug

Mar 2005:

FDA

Sept 2006:

IOM

and P

Mar 2007:

FDA

Comm

June 2007:

Public RISKMAP workshop

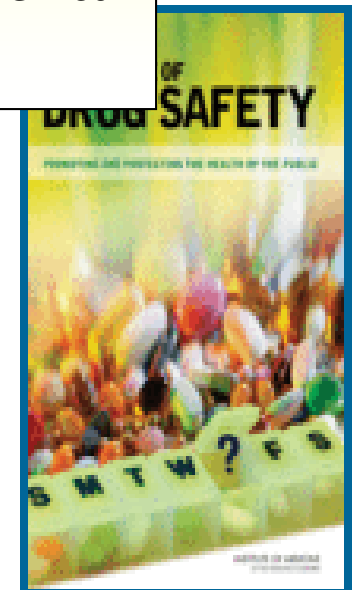
Sept 2007:

PDUFA (IV) / FDAAA

Amended Federal Food, Drug, and Cosmetic Act (FDCA)

Provided FDA the legal authority to require **risk evaluation and mitigation strategies (REMS)** for applicable drugs

- May not introduce drug into interstate commerce if in violation of provisions
- Drug may be found to be misbranded
- FDA can impose civil penalties for violations of the Act



Restricted Distribution Programs Prior to FDAAA

• 1988:	Isotretinoin*	• 2002:	Alosetron
• 1989:	Clozapine	• 2002:	Sodium oxybate
• 1998:	Thalidomide Fentanyl citrate	• 2003:	Abarelix
		• 2005:	Lenalidomide
• 1999:	Dofetilide	• 2006:	Natalizumab Fentanyl PCA
• 2000:	Mifepristone		
• 2001:	Bosentan	• 2007:	Ambrisentan Small pox (Vaccinia) Vaccine

* *RiskMAP for isotretinoin was approved in 1988 and revised in 2002 & 2005.*

Knowledge Check



REMS came into existence via which of the following pieces of legislation:

- A. FDA Amendments Act of 2007
- B. Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012
- C. FDA Compliance Regulation of 1997
- D. Omnibus Budget Reconciliation Act of 1990

Knowledge Check



REMS came into existence via which of the following pieces of legislation:

- A. **FDA Amendments Act of 2007**
- B. Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012
- C. FDA Compliance Regulation of 1997
- D. Omnibus Budget Reconciliation Act of 1990

Risk Evaluation and Mitigation Strategy (REMS)



- A required risk management plan that uses risk mitigation strategies beyond FDA-approved FDA professional labeling.
- FDA Amendments Act of 2007 authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
- Applies to NDAs, BLAs, and ANDAs.
- REMS can be required pre- or post-approval.

xx6

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xx6

FDA does not regulate the practice of medicine,

REMOVE THE bullet but you can speak to this

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Risk Evaluation and Mitigation Strategy (REMS) - continued



- Designed to achieve specific goals to mitigate risks associated with use of a drug.
- FDA specifies the required elements of a REMS.
- Drug sponsors develop the REMS program based on required elements. FDA reviews and approves the REMS.
- Each REMS has specific safety measures that are targeted to the serious risk(s) associated with the drug or class of drugs.
- All REMS include elements, communication, and/or educational materials to communicate risk information to various stakeholders.

Considerations in determining the need for a REMS



- Estimated size of the population likely to use the drug
- Seriousness of the disease or condition being treated
- Expected benefit of the drug
- Duration of treatment
- Seriousness of any known or potential adverse effects
- Drug is a new molecular entity



Possible Components of a REMS

- A REMS can include
 - Medication Guide or Patient Package Insert
 - Communication Plan for Healthcare Provider^c (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. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS*

Medication Guides



- Provide FDA approved patient-friendly labeling
- Can be required as part of labeling, if FDA determines one or more:
 - Patient labeling could help prevent serious adverse events
 - The product has serious risks that could affect patient’s decision to use or continue to use
 - Patient adherence to directions is crucial to product effectiveness
- To be included in the REMS, it must be determined that the MG is necessary to ensure the benefits outweigh the risks- it can be a REMS element or a tool under another element of the REMS*

* *February 2011 Guidance available at:*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf>

Communication Plans (CP)



- Directed to healthcare professionals.
- Provide information about REMS-related serious risks of the drug and any methods to assure safe use and can serve to disseminate information about the REMS to encourage implementation.
- When a generic application is approved, FDA must implement the CP for both the innovator and the generic

REMS Communication Tools xx7



- Letters
 - Healthcare Professional
 - Professional Society
- Fact Sheets
- REMS-dedicated Websites
- Informational slide deck/webinars
- Journals Information pieces
- Patient counseling tools
- Training Programs
- Informational brochures
- Field representatives/medical liaisons
- Outreach to professional organizations
- Call Center or Medical Information Department
- Wallet Card
- Patient- Provider Acknowledgements
- Prescription Authorization Forms
- Enrollment forms (prescriber, pharmacist, patient)

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xx7

I removed the footer it was from an older presentation

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Elements to Assure Safe Use (ETASU)



- Purpose of REMS with ETASU FDAAA Title IX Section 901 505-1 f(1)(A)
 - (f) Providing Safe Access For Patients To Drugs With Known Serious Risks That Would Otherwise Be Unavailable**
 - (1)(A) the drug, which has been shown to be effective, but is associated with a serious adverse drug experience, can be approved or would otherwise be withdrawn from the market if such elements are required as part of the strategy to mitigate a specific serious risk listed in the labeling of the drug.

Elements to Assure Safe Use (ETASU)



- REMS may include one or more ETASU:
 - health care providers who prescribe the drug have particular training or experience, or are specially certified
 - Pharmacists or other dispensers be specially certified
 - Drug be dispensed only in certain healthcare settings (e.g., infusion centers, hospitals)
 - Drug be dispensed with evidence of safe-use conditions
 - Each patient using the drug be subject to monitoring
 - Each patient using the drug be enrolled in a registry



Implementation Systems

- REMS may include an implementation system related to these ETASUs:
 - Certification of pharmacies and hospitals
 - Restricted use to certain healthcare settings
 - Documentation of safe use conditions
- May require applicant to take reasonable steps to:
 - Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and
 - Work to improve implementation of such elements by such persons

Timetable for Submission of Assessments



- REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS
- The timetable for submission of assessments must include an assessment
 - by 18 months,
 - by 3 years, and
 - in the 7th year after the REMS is initially approved



REMS Assessment Plan

- Objective: To determine whether the REMS is meeting its goal(s) and whether one or more such goals or elements should be modified.
- Modifications may be required if a REMS is not meeting its goals or in order to minimize the burden on the healthcare delivery system of complying with the REMS.



Information that may be used to assess REMS

- A survey to evaluate patients' or HCPs' knowledge of the serious risks or measures that need to be taken to mitigate risk
- Enrollment/certification statistics kept by company
- Information about use patterns of the drug including:
 - Use by prescriber specialty
 - Patient-level data (age, gender, race)
 - Length of therapy
 - Indication
 - Concomitant drug therapy



Information that might be used to assess REMS (continued)

- Population-based administrative or claims-based data to measure rates of specified serious adverse events
- Active surveillance using sentinel reporting sites to determine rates of specified serious adverse events
- Summaries of specific adverse events collected spontaneously



Knowledge Check

Considerations in determining the need for a REMS include the following:

- A. Duration of treatment
- B. Estimated Size of the Population expected to use the drug
- C. Patent status of the molecule
- D. Both A & B



Knowledge Check

Considerations in determining the need for a REMS include the following:

- A. Duration of treatment
- B. Estimated Size of the Population expected to use the drug
- C. Patent status of the molecule
- D. Both A & B**



Knowledge Check

Potential Elements of a REMS include:

- A. Communication Plan
- B. Medication Guide
- C. Elements to Assure Safe Use
- D. All of the above



Knowledge Check

Potential Elements of a REMS include:

- A. Communication Plan
- B. Medication Guide
- C. Elements to Assure Safe Use
- D. All of the above**

Knowledge Check



Assessments of REMS must be completed by:

- A. 18 months post approval
- B. 3 years post approval
- C. 7 years post approval
- D. A, B and C, if the REMS is not released by Year 3

Knowledge Check



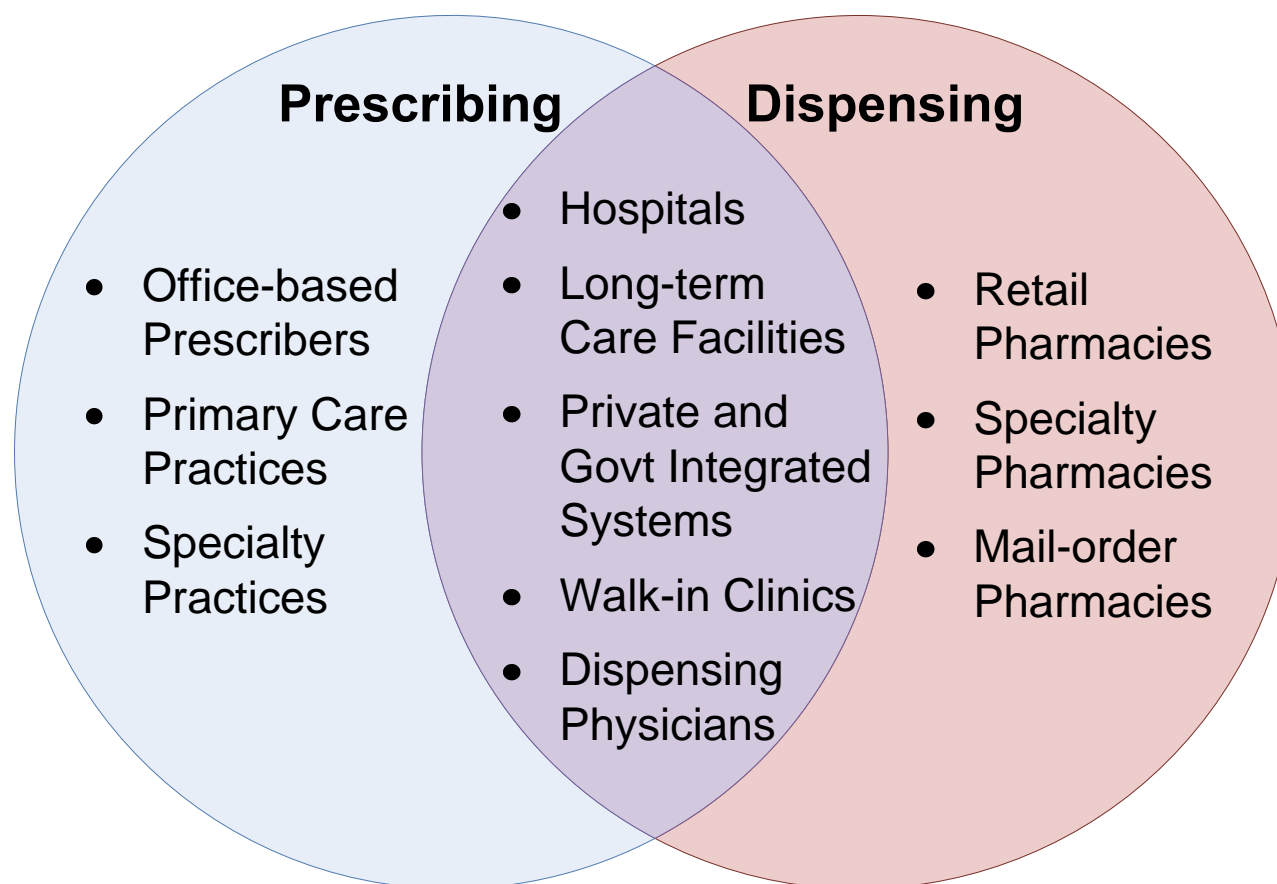
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Examples of REMS: An in-depth look

Diversity in our Healthcare System





Addyi (flibanserin)

REMS goal:	Mitigate the increased risk of hypotension and syncope associated with DDI between Addyi and alcohol
Outpatient pharmacy requirements:	Complete staff training, verify prescriber is certified, obtain authorization to dispense, and counsel patient prior to dispensing
Inpatient pharmacy requirements:	Dispense for inpatient use only

Tracleer (bosentan)



REMS goal:	Minimize the risks of hepatotoxicity and fetal exposure by informing prescribers, patients, and pharmacists about the risks of Tracleer and its safe-use conditions
Outpatient pharmacy requirements:	Ensure patient counseling, verify LFT and pregnancy testing (for FRPs) completed, obtain authorization to dispense, dispense no more than 30 days' supply
Inpatient pharmacy requirements:	Obtain authorization to dispense, dispense no more than 15 days' supply

Lemtrada (alemtuzumab) xx8



REMS goal:	Mitigate the risk of autoimmune conditions, infusion reactions, and malignancies associated with Lemtrada.
Pharmacy requirements:	Enroll; verify order form received, prescriber certified, infusion site certified, and patient enrolled and authorized
Infusion center requirements:	Enroll; ensure appropriate personnel and equipment on-site, counsel patient, obtain order form and authorization to dispense/infuse, assess patient for infusion reactions during and 2 hours after infusion, complete and submit Infusion Checklist to the sponsor

Slide 47

xx8

Consdier only using 2 examples. You ahve a lot of slides. I am, not sure you will get through all of them

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Knowledge Check



The REMS dispensing ETASU applies only to pharmacies that dispense the drug: True or False?

- A. True
- B. False

Knowledge Check



The REMS dispensing ETASU applies only to pharmacies that dispense the drug: True or False?

- A. True
- B. False**



Summary

- Risk management continues throughout the lifecycle of a product
- For the majority of approved products, labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits
- Tools selected for a risk management program are product specific xx9
- REMS contain elements and appended materials to mitigate specific risks associated with a drug
- In developing a REMS, one important consideration is diversity in dispensing. xx10

Slide 50

xx9 product and risk specific
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xx10 what do you mean
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The End