REMS: Why They Matter

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Continuing Education

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Accreditation:
The National Pharmacy Technician Association (NPTA) is accredited by the Accreditation Council for Pharmacy Education (ACPE) is an approved provider of continuing pharmacy education.

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Learning Objectives

At the end of this presentation, the alert attendee should be able to:

- define REMS and explain why they are established.
- discuss the legal authority in REMS.
- analyze the incentives or goals of REMS program(s).
- describe the overall process of REMS.
- identify the different stakeholders and their roles.
- determine REMS' effectiveness and assess if REMS really do matter.

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What is REMS?

- **R**isk **E**valuation and **M**itigation **S**trategies (REMS)
- Patient safety program implemented to ensure that the benefits of a drug or biological product (biologic) outweigh its risks.
- Specific brand or generic drug
- Individual drug or class of drugs

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REMS Historical Timeline

- REMS was initiated in the 1960s due to Thalidomide medical tragedy of the 1950s (birth defects)
- 1970s, the Controlled Substance Act was enacted and imposed regulations on medication with high abuse-potential, thus creating the "Patient Package Insert"
- 1980s and into the 1990s, certain medication began to adopt safety programs that accompanied their use:
  - 1988 – Pregnancy Prevention Program for Accutane: users had to satisfy Pregnancy Prevention Program (iPLEDGE) before receiving medication.

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REMS Historical Timeline (Cont'd)

  - 1990 – "No blood, no drug" program was initiated for Clozaril due to the potential for agranulocytosis.
- 2004, Risk Management Programs (RMPs) or Risk Minimization Action Plans (RiskMAPs) were introduced by the FDA who occasionally requested companies to develop special safety programs to minimize serious risks for a limited number of drug products that had usually high risks but offered substantial therapeutic benefits.

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Legal Authority

- In 2007, FDA received expanded risk management authority through the FDAAA (Section 505-1 of the FD&C Act) to require a REMS when necessary, to ensure the benefits outweigh the risk of a drug.
- REMS are designed to ensure medication use conformity that support the safe use of medication: prescribing, dispensing, administering and monitoring.
- REMS are not intended to mitigate all the adverse events of a medication.
- REMS are required when certain specific risks exist that might otherwise limit the approvability and use of a medication.

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Determining Factors Requiring REMS

- Before approval, during clinical trials if the FDA determines a REMS is necessary to ensure the benefits of a drug or biologic outweighs the risks.
- Post-approval (drug on market), if the FDA becomes aware of risk through clinical experience.
- Pharmaceutical manufacturers (drug sponsors) submission of a NDA, due to new drug (NME) or BLA as part of initial approval or licensing due to new product indication or when new safety information occurs.

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Other Factors Considered

- Severity of the disease
- Anticipated drug benefits
- Anticipated duration of treatment
- Severity of known or potential adverse events
- Population size likely to use the drug

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What is the Functionality of REMS

- The FDA determines a REMS is needed
  - When a new medication is submitted to FDA or new adverse event is reported, the FDA will evaluate the benefit/risk balance and determine if a REMS is required.
- Drug sponsor develops a specific REMS program
  - Program needs to have a risk mitigation strategy: an achievement plan and how it is to be accomplished.
  - To include an assessment timeframe, to ensure that the REMS program is meeting its goal.

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What is the Functionality of REMS (Cont'd)

- FDA Reviewal and Approval of REMS Program
  - Proposed program is submitted and reviewed by FDA. If it meets FDA safety requirements, REMS program is approved.
- Drug Sponsor implements the REMS program with different stakeholders (participants).
  - The drug sponsor communicates with the different participants involved in the healthcare delivery process.

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Stakeholders (participants) and Their Roles

- Patients and caregivers:
  - Patients have an essential role in REMS. They may be required to enroll in the REMS program and for some medication, must sign a form acknowledging that they understand those risks before starting the medication.
  - It is important for patients to follow any requirements to ensure that there is no delay or discontinuing of treatment.
  - Patients may also participate in surveys about the REMS.

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Stakeholders (participants) and Their Roles (Cont'd)

- Survey helps the FDA to evaluate the effectiveness of the REMS.
- Healthcare providers:
- Those with prescribing privileges must ensure products with serious risks requiring REMS are prescribed and used safely.
- The requirements for healthcare providers will vary for each REMS.
- Providers may need to be trained or certified to prescribe.

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Stakeholders (participants) and Their Roles (Cont'd)

- Pharmacies and other healthcare facilities:
- Have the responsibility of ensuring that products with serious risk requiring REMS are dispensed and used safely.
- REMS is rarely the same
- The requirements for a pharmacy or other healthcare facility may vary
- For pharmacies, the drug sponsor prefer to restrict distributions of certain REMS program to specialty pharmacies.

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Stakeholders (participants) and Their Roles (Cont'd)

- Specialty pharmacies have the expertise to manage the drugs in a matter that reduces risks to patients and liability potential to the pharmaceutical manufacturers.
- Pharmacists are subject to verification and receive training and instruction regarding the distinctive effects of REMS drugs that may vary from drug to drug.
- Trained pharmacists are able to manage the complexity of REMS requirements of drugs.

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Possible Elements or Components of a REMS

A REMS can consist of one or more of the following:

- Medication Guide (MG) or Patient Package Insert
- Communication Plan (CP)
- Elements to Assure Safe Use (ETASU)
- Implementation Plan or system

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Medication Guide

- FDA approved documents or handouts that address important safety information that is specific to a particular drug or drug class that can help patients avoid serious adverse events.
- Written in non-technical language or jargon (layman terms)
- Must be provided to patients by the pharmacy each time the medication is dispensed.

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Medication Guide REM Example

- Tracleer (Bosentan)

- objective: to inform of the risks of toxicity to the liver and birth defects

- Lotronex (Alosetron)

- objective: to inform of the risks of inflammation in the large intestine or colon and serious Complications of Constipation (CoC).

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Communication Plan

A plan or strategy to educate healthcare professionals on the safe and appropriate use of the drug

- Materials and tools used may include:
  - "Dear Healthcare Professional" letters
  - Factsheets
  - Journal information pieces
  - Websites

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Communication Plan Example

- Aveed (Testosterone Undecanoate)
  - Objective: to inform healthcare providers that Aveed can cause Pulmonary oil micro-embolism (POME) and anaphylaxis, which have the potential to lead to serious medical consequences, such as respiratory distress and syncope.
- Caprelsa (Vandetanib)
  - Objective: to inform healthcare providers of the serious risks of QT prolongation, Torsades de Pointes, and sudden death.
  - The need to monitor for QT prolongation and electrolyte abnormalities.

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Elements to Assure Safe Use (ETASU)

Not all REMS programs have an ETASU. For those that do, there are specific interventions or requirements implemented to enforce the appropriate use of a drug before healthcare providers can prescribe or dispense a medication.

- ETASU may be necessary throughout the course of treatment.

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Possible ETASU Risk Dependent Requirements

1. Specialized training or certification of healthcare providers who prescribe the drug
2. Certification of pharmacies or healthcare facilities (dispensers)
3. Limited or restricted dispensing/administration settings, such as specialty pharmacies, infusion settings, and hospitals
4. Documented evidence of safe-use conditions before dispensing/administration, such as lab test results
5. Patients are subject to certain monitoring
6. Registry enrollment for patient

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ETASU REM Example

- Soliris (Eculizumab)
  - ➢ Used to treat paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS)
  - ➢ Risks of serious infections, particularly meningococcal infection and Progressive multifocal leukoencephalopathy (PML)
- ETASU:
  - Prescriber certification
  - All prescribers must enroll with the manufacturer

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ETASU REM Example (Cont'd)

- ETASU:
  - Manufacturer is responsible for providing education to certified prescribers annually, ensuring that Eculizumab is distributed only to certified prescribers and that prescribers comply with REMS requirements.

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ETASU REM Example

- Xyrem (Sodium Oxybate)
  - ➢Used to treat cataplexy and narcolepsy
- ETASU
  - Prescriber certified
  - Pharmacy certification
  - Patient enrollment with documentation of safe use conditions

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Implementation Plan or System

- Used to monitor and evaluate participants who are responsible for implementing certain ETASU.
- To collect data to determine whether a REMS was successful or if modification is necessary.

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Timetable for Submission of Assessments

- Every proposed REMS for an NDA or BLA product must have a timetable for submission of REMS assessment that meets two parameters (505-1(g) FD&C Act):

1. Assessment submitted to FDA:
   a. By 18 months after the strategy is initially approved
   b. Three years after the strategy is initially approved

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Timetable for Submission of Assessments (Cont'd)

c. In the 7th year after the strategy is initially approved.

2. Frequency specified can be increased or decreased under certain circumstances and/or eliminated under certain circumstances.

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FDA Approved REMS Since Implementation of FDAAA

Currently, there are 63 REMS. The breakdown of number and percentages, including elements which are MG, CP, and ETASU are as follows:

- 57 (90%) include ETASU
- 4 (6%) include CP
- 1 (2%) include MG
- 1 (2%) include CP and MG

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Generic Drug Protocol

- Hatch-Waxman Act created a pathway for generic drugs
- Allows a generic drug manufacturer to submit an Abbreviated New Drug Application (ANDA)
- Generic drug must demonstrate that it is the same as the brand drug (Reference Listed Drug or RLD)
- Generic drug must consist of the same active ingredients, strength, dosage form, and ROA as the brand drug.
- Must be bioequivalent
- Meet other requirements: chemistry, manufacturing, controls, labeling, and testing.

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REMS requirement for Generic Drugs

- Current law requires RLD to be subject to REMS, ANDA referencing the product is subject to two of the REMS components:
  1. MG or package insert
  2. ETASU
- Generic and RLD must enter into a Single, Shared System (SSS) of ETASU (unless the FDA waives this requirement for the generic drug allowing the generic drug to use a separate, comparable REMS program)

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Possible Reasons for Waiver

- Creating a SSS outweighs the benefit (taking into consideration the impact on healthcare providers, patients, generic applicants and the RLD holder.
- An aspect of the ETASU has an unexpired patent.
- A method entitled to protection (trade secret) and the generic applicant certifies that it sought a license for use of the ETASU aspect and was unable to obtain license.

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REMS process of Developing a SSS

- Begins with the Office of Generic Drugs (OGD), which first notifies the ANDA sponsor of the requirements (REMS notification letter)
- ANDA applicant sponsor contact RLD holder
- FDA kick-off meeting (convey expectations and facilitate development of SSS)
- Generic developer and RLD holder form Industry Working Group (IWG)
- IWG develop a proposal for SSS REMS
- RLD holder and ANDA sponsor submit REMS proposal for FDA review

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Negotiations related to SSS REMS Program

- Cost-sharing
- Confidentiality
- Product liability
- Antitrust concerns
- Assess to a license for elements protected by a patent

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Complications of Negotiations

- Due to concerns the FDA and generic drug industry have expressed regarding brand companies impeding the development of a SSS, brand companies have indicated that negotiations with SSS REMS are complicated.
- Due to involvement with important safety issues and a complex healthcare system.
- Time-consuming process for IWG to reach agreements on issues:

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Complications of Negotiations (Cont'd)

a. Assessments
b. Adverse event reporting protocols
c. Collective standard operating procedures
d. Cost-sharing
e. Decision-making authority about REMS administration
f. Modification
g. REMS design
h. Associated legal issues (product liability and intellectual property)

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Benefits of SSS

- Reduces encumbrance for stakeholders by:
  - Single portal to access documentation and materials
  - Prescribers, pharmacies, and healthcare settings to complete certification and other requirements once rather than independently for brand and generic drugs

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Opioids: REMS Class of Drugs

- Opioid analgesics, brand name, and generic pain-reducing medication that bind to opioid receptors in the body.
- Necessary component of pain management for certain patients
- Therapeutic benefits when used properly
- Serious risks
- Abuse, misuse, overdose
- Insufficiency, regardless of additional warnings on the label, risk management plans, and inter-agency collaborations

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REMS and Opioids

- Opioid crisis
- FDA uses REMS as tools to mitigate misuse and abuse of opioids
- February 2009, FDA sent letters to manufacturers of extended-release, long-acting (ER/LA) opioids indicating that REMS would be required to ensure that the benefits of this class of medication continue to outweigh the risks.
- July 2012, REMS for ER/LA opioids was initially approved and has been updated on following occasions
- 2017, FDA announced that immediate-release (IR) opioids would require the same REMS requirement as ER/LA opioids

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REMS and Opioids (Cont'd)

- REMS include an MG
- ETASU that requires covered manufacturers to provide training to health care providers and a Timetable for Submission of Assessments

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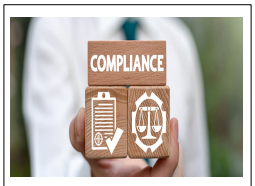
How Effective is REMS?

- Office of the Inspector General (OIG) for the Department of Health and Human Services (HHS) report
- FDA has limited data to determine whether REMS improved drug safety to minimize burdens on patients and the health care system.
- Report findings cause concern for OIG "regarding the overall effectiveness of the REMS program"



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OIG Recommendations

- A developed and implemented plan to identify, validate and assess REMS components.
- Seven recommendations:
  1. "Clarify expectations for sponsors' assessments in FDA assessment plans
  2. Evaluate the ETASUs of one REMS each year as required by law
  3. Ensure that assessment reviews are timely
  4. Identify incomplete sponsor assessments and work with sponsors to obtain missing information
  5. Identify REMS that are not meeting their goals and take appropriate actions to protect the public health
  6. Seek legislative authority to enforce FDA assessment plans"

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REMS and Why They Matter
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3. Do REMS really matter?
a. Yes
b. No
c. I do not know

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Questions…

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