Orientation to Risk Evaluation and Mitigation Strategies (REMS)

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Background

- The REMS provisions of the 2007 Food and Drug Administration Amendments Act (FDAAA) give FDA authority to require REMS if the Agency determines that a REMS is needed to ensure the benefits of the drug outweigh the risk.

- The REMS authority enables FDA to approve, and patients to have access to, certain drugs whose risks would otherwise exceed their benefits and may not be approvable.

- For the majority of approved products, FDA has determined that product labeling and routine AE reporting are sufficient and a REMS is not necessary to ensure a product’s benefits outweigh its risks.
Background (2)

- By their nature, all REMS impose some burden on the healthcare system but they vary in how much.
  - multiple REMS place further burdens on the healthcare system.
  - classwide and shared system REMS have partially offset this

- Changes could be made to REMS to improve their efficiency and reduce burdens on the healthcare system.
  - standardization
  - integration

- PDUFA user fees provide support for enhancing REMS by
  - measuring their effectiveness and
  - evaluating, with stakeholder input, appropriate ways to better integrate REMS into the existing and evolving healthcare system.
What is a REMS

- A REMS is a healthcare intervention plan/program that is designed, implemented and assessed as follows:
What is a REMS (2)

- REMS include goals/objectives e.g., To mitigate the risk of [a serious AE] by...
  - (1) informing, educating and/or training
  - (2) facilitating, enabling, and/or coordinating
  - (3) managing, controlling and/or ensuring safer medication use

- They are comprised of a set of elements/tools
  - Patient-directed tools, e.g., Medication Guide, counseling sheet, website, physician-patient agreement, enrollment form
  - Physician/pharmacist directed tools, e.g., Letters, training, certification/enrollment form, CME, website, requirements
  - Setting/supply chain tools, e.g., Certification requirements, forms (safe use conditions), tracking

- They are assessed at a minimum of 18, 36 and 84 months
REMS Have Been Used Selectively

- About 200 REMS have been approved since 2008.
- Many were “MedGuide only” REMS which have been released.
- As of July 2013, there are 72 REMS.
  - 66 individual drugs
  - 6 shared system REMS including 84 applications (NDA and ANDA)

Types of REMS (N= 70*)

*Numbers as of June 2013
How REMS Have Varied

• Goals - some goals have been more general and others more specific
  – e.g., “to inform patients about the risks of Drug X”
  – e.g., “to mitigate the risk of Y associated with Drug X”

• Design –
  – targeted stakeholder(s); some include both patients and prescribers, others only include prescribers
  – variation in the element(s) used to address a given risk
    • e.g., for a given risk some REMS have required restrictions while others have not
How REMS Have Varied

- Selection of tools –
  - Patient directed tools have included Medication Guides, Patient Guides, Booklets, Brochures, Counseling Tools, Patient-Prescriber Agreement Form (PPAF), Patient Enrollment Form, REMS-dedicated Website
  - Prescriber directed tools have included REMS training materials, Prescriber Guides, Booklets, Brochures, Counseling Tools, Patient-Prescriber Agreement Form (PPAF), Prescriber Enrollment Form, REMS-dedicated Website
  - Dispensing settings have varied in degree of certification

- Assessment plan – metrics, data sources, data to inform redesign e.g., RCA
Diverse Factors Contribute to REMS Variation (Goals, Design, Tools)

- Degree of hazard
- Preventability (risk factors)
- Detectability
- Reversibility
- Temporality

- Sponsor proposals
- Regulatory constraints
- Lack of evidence
- Healthcare system gaps
- Precedent inconsistencies
- Unmet needs
- Burden/access
- Cost
Variations Between REMS

• Explained/necessary variations e.g.,
  – Risks and circumstances vary requiring a degree of customization
  – Addressing diverse healthcare system with one single program design
  – Dispensing restrictions may be detrimental in some cases (anti-rejection)
  – Subpopulations may be at unequal risk (teratogens)
  – New legislation, new technology, new field

• Unexplained/unnecessary variations e.g.,
  – Human factors
  – Sponsor proposal have varied
  – Approaches to educating prescribers (training, attestation, certification)
  – Differing instructions for similar risks
  – Limitations to assessment methods and data
  – Other
Opportunities to Standardize REMS

- Extent of AE risk characterization
- Application of standard criteria for requiring a REMS
- Systematic use of prospective “failure analysis” methods to inform:
  - Descriptions of desired program goals/objectives
  - REMS program design/re-design
  - Consistent selection and implementation of tools from a standardized REMS “toolkit” to each stakeholder
  - Assessment metrics and methods
REMS Integration Initiative – Structure

REMS Integration Steering Committee (RISC)

REMS Policy Workgroup
Develop principles for how to apply the statutory criteria to determine whether a REMS is necessary and other factors associated with requiring a REMS.

REMS Design and Standardization Workgroup
Develop an analytically rigorous approach to designing, standardizing and integrating REMS programs.

REMS Evaluation Workgroup
Develop a consistent and evidence-based approach for evaluating the effectiveness of REMS programs and their burden on healthcare delivery systems.
Ideal Future State

- Fully characterized AE risk
  - At risk pop.
  - Detectability
  - Temporality
  - Mitigability
  - Reversability

- Prospective Failure Analysis
  - Systematic
  - Evidence based
  - Stakeholders
  - Failures specify targets

- Goals & Objectives
  - Consistent
  - Specific
  - Measurable

- Standardized REMS Toolkit
  - By stakeholder
  - Integrated
  - Content/enablers
  - Nonburdensome

- Standardized Assessments
  - Metrics
  - Systems
  - Domains
  - Inform
BackUp
Patient-Directed REMS Tools

- Medication Guides (MG)
- REMS Print Materials
  - Patient Guides, Booklets, Overviews, Brochures
  - Counseling Tools (*may be part of prescriber/healthcare provider materials*)
- Patient-Prescriber Agreement Form (PPAF)
- Patient Enrollment Form
- REMS-dedicated Website
Patient-Directed REMS Tools (1)

- **Medication Guides (MG)**
  - The most frequently-used patient educational materials in REMS
- **Purpose**: To provide information when the FDA determines in writing that it is necessary to patients’ safe and effective use of drug products
  - **Length**: 1 - 8 pages
  - **Format**: Text, bullets
  - **Delivery Method**: Provided to patient by pharmacist or healthcare provider, or accessed by the patient online
Patient-Directed REMS Tools (2)

- **REMS Print Materials**
  
  Patient Guides, Booklets, Overviews, Brochures

  **Purpose:** Focus on REMS risks and REMS program information

  **Length:** 2 - 18 pages

  **Format:** Text, bullets, tables, graphics

  **Delivery Method:** Provided to patient by healthcare provider.
  Can also be downloaded from REMS-dedicated website
Patient-Directed REMS Tools (3)

Counseling Tools for Healthcare Providers (Print materials)

**Purpose**: Tools used by healthcare providers to counsel patients about safe use of drug

– Include risks of the drug, patient responsibilities, and encourage patient-prescriber discussion

**Length**: 1 - 2 pages

**Format**: Text, bullets, tables

**Delivery Method**: Provided to patient by healthcare provider
Patient-Directed REMS Tools (4)

- **Patient-Prescriber Agreement Forms**
  - **Purpose**: Used to document that an informed discussion of the drug’s benefits and risks took place and that the patient understands the risks and REMS program requirements
  - Supports patient counseling by providing information for prescribers to review with patients
  - **Length**: 1-2 pages
  - **Format**: Text, bullets
  - **Delivery Method**: Provided to patient by prescriber
Patient-Directed REMS Tools (5)

• **Patient Enrollment Forms**
  
  **Purpose:** Contain agreements and acknowledgements of safe use conditions
  
  – Used to enroll patients into REMS program in order to receive drug
  – Allows sponsor to track patients and ensure that only those who have completed the form can obtain drug

  **Length:** 1-2 pages
  
  **Format:** Text, bullets
  
  **Delivery Method:** Provided to patient by healthcare provider
Prescriber Tools for REMS (1)

- Product labeling
- REMS program communications
- REMS training materials
- Additional REMS materials
- Enrollment forms to support certification
Prescriber Tools (2)

REMS Program Communications

**Purpose:** Deliver messages to healthcare providers about drug risks and REMS programs

**Examples:** Dear Healthcare Provider Letters and e-mails, letters to professional societies, factsheets, REMS-dedicated websites, journal information pieces
Prescriber Tools (3)

Training Materials

Purpose:
- Provide comprehensive training on risks addressed in REMS and how to mitigate risks
- Explain how the REMS program operates
- Describe prescriber roles/requirements

Examples:  Program Overviews, Prescriber Guides, Training Modules

Delivery:  In person, by phone, print, electronic (online/DVD), with or without audio
Prescriber Tools (4)

Additional Materials

**Purpose:** Address specific issues related to safe use of drug; enabling tools to support ongoing patient care

**Examples:** Checklists, counseling tools, dosing and administration guides

Enrollment Forms

**Purpose:** Enroll prescriber into REMS program

**Content:** Prescriber demographic information, acknowledgements, agreements
Role of Dispensers/Dispensing Settings in REMS

REMS may require that:

• practitioners or settings that dispense the drug are specially certified

• the drug is dispensed only in certain healthcare settings

• the drug is only dispensed to patients with evidence or documentation of safe-use conditions
REMS Requirements for Dispensers

(1) To be certified to dispense, dispensers may be required to:

• Designate “Authorized Party”
• Train and/or ensure staff are trained
• Enroll
• Establish systems for tracking and/or document management
• Modify existing systems and/or processes (electronic and/or manual)
REMS Requirements for Dispensers

At the time of dispensing, dispensers may be required to:

- Verify ‘documentation of safe use conditions’
  - Record/document verification
  - Resolve verification failures
- Provide Medication Guide
- Counsel patients and/or caregivers
REMS Requirements for Dispensers

(3)

Periodically, dispensers may be required to:

• Re-enroll
• Train new staff
• Participate in audits
• Implement new or modified REMS requirements
Towards a Systematic Approach to REMS Design

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Why do we need a systematic approach to REMS design?

A systematic approach to REMS design could help us...

- Document and communicate a “rationale” for each REMS.
- Comprehensively identify and anticipate failures.
- Address complexity of drug risk management.
- Reduce unnecessary variation in REMS design and tools.
- Increase predictability of review process.
REMS Design: Future State

Establish the Scope

- Characterize the risk that the REMS is trying to address and conditions for safe use of the drug.
- Establish the likely context of use for the drug.

Analyze the Problem

- Identify failures in safe use that might lead to patient harm.
- Identify underlying causes of those failures.

Specify Interventions

- Specify key information / desired behaviors / process changes to address underlying causes.
- Develop interventions to convey information/behaviors.
Characterize the risk and safe use of the drug

- How do patients become exposed to the risk?
- What is the relationship between exposure and the adverse reaction of concern?
- Can exposure be managed to reduce the likelihood of an adverse reaction? How?

- What is the adverse reaction (ADR) of concern?
- Can it be prevented, detected, or treated? How?
- What risk factors affect the likelihood of an ADR?
- Can they be prevented, detected, or treated? How?

- What are adverse outcomes that can result and how likely/severe are they?
- What factors affect their likelihood/severity?
- Can they be prevented, detected, or treated? How?
Establish the context of use

- Which patient populations that are likely to use the drug?
- In which healthcare settings is the drug likely to be prescribed?
- Which stakeholders will be involved in the patient’s care?
- What is the process by which the patient is treated?

Medication Use Process

1. Patient Selection
2. Prescribing
3. Dispensing
4. Administration
5. Monitoring
Identify possible failures

- What are the potential failures that could lead to unsafe use and patient harm?
- Where in the medication use process could these failures occur?
Identify underlying causes of failure

- How does the medication use process contribute to the failure?
- How do the knowledge, attitudes, beliefs, and behaviors of stakeholders contribute to the failure?
Identify key information, desired behaviors, interventions

- What information, behavior changes, or process changes are needed to address the underlying causes of failure?
- What interventions can effectively convey information and implement changes?

**Medication Use Process**

- Patient Selection
- Prescribing
- Dispensing
- Administration
- Monitoring

- Intervention
- Failure

- Intervention
- Failure

- Intervention
- Failure

- Intervention
- Failure

- Intervention
- Failure
Develop tools

- When is it possible to use engineering or administrative controls?
- How do we balance tool “intensity” against access and burden considerations?
Use tools from a standard REMS “toolkit”

- What tools can we use from our REMS toolkit?
- How should they be customized to the individual REMS?
Practical Considerations

An effective approach should...

1. Work within the regulatory review process
   - Build an evidence base that permits informed decision-making
   - Consider time/resource and regulatory constraints

2. Focus on what’s most important
   - Prioritize most important failures, root causes
   - Prioritize most effective/feasible interventions

3. Streamline to enhance efficiency
   - Share tools across programs
     (e.g., for similar risks, failures, and/or contexts of use)
   - Re-use analysis across programs

4. Design with evaluation in mind