
REMS Update

PDUFA Stakeholder Meeting
March 8, 2013

Outline

- REMS 101
 - Authorities, requirements and policies
 - REMS elements
 - REMS assessments
- FDA's REMS Integration Initiative
 - Background
 - Goals
 - Structure, deliverables and stakeholder outreach

REMS 101: Authorities, Requirements and Policies

- REMS = risk evaluation and mitigation strategy
- FDA Amendments Act (2007) authorized FDA to require REMS.
- REMS are required risk management plans that use risk mitigation strategies beyond professional labeling to ensure that the benefits of prescription drugs outweigh their risks.
- FDA can require a REMS before or after a drug is approved.

REMS 101: Authorities, Requirements and Policies (cont.)

- FDA specifies the required elements of a REMS.
- Drug sponsors develop the REMS program based on required elements. FDA reviews and approves the REMS.
- Under a REMS, healthcare professionals may need to follow specific procedures to safely prescribe, dispense, administer or distribute a drug.
- Patients may need to enroll in the REMS program or receive special counseling.
- Each REMS has specific safety measures that are targeted to the serious risk(s) associated with the drug or class of drugs.

Approved REMS

The screenshot shows the FDA website's 'Approved Risk Evaluation and Mitigation Strategies (REMS)' page. The page title is 'Approved Risk Evaluation and Mitigation Strategies (REMS)'. Below the title, there is a brief explanation of REMS and a list of categories: 'Currently Approved Individual REMS', 'Currently Approved Shared System REMS', and 'Released REMS'. The 'Currently Approved Individual REMS' section contains a table with the following data:

Product	Application	Date REMS Approved	REMS Components (All REMS include timetable for assessment)
Ademtra (tocilizumab) Injection (PDF - 2MB)	BLA 125276/49	1/8/2011; modified 4/15/2011, 6/20/2012, 10/11/2012	communication plan
Adasuve (loxapine) Inhalation Powder (PDF - 3.5MB)	NDA 22-549	12/21/2012	communication plan, elements to assure safe use, implementation system
Ampyra (dalfampridine) Extended-Release Tablets (PDF - 124KB)	NDA 22-250/S-004	1/22/2010; modified 11/17/2011; 7/20/2012	communication plan

- About 200 REMS have been approved since 2008.
- Many of these were “MedGuide only” REMS which have since been released.
- Today there are about 74 REMS.

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

REMS 101: Statutory factors considered by FDA when determining the need for a REMS



Size of the population likely to use the drug



Seriousness of the disease/condition to be treated



Expected benefit of the drug



Expected duration of treatment



Seriousness of known or potential adverse events



Whether the drug is a new molecular entity (NME)

REMS 101: REMS Elements

All REMS required for an NDA or BLA product must contain a timetable for submission of assessments of the REMS.

A REMS for an NDA or BLA product may also contain any of the following elements:

- Medication Guide or Patient Package Insert
- Communication Plan
- Elements To Assure Safe Use (ETASU)
- Implementation System

REMS for ANDA (generic) products may contain the following:

- Medication Guide
- Elements to Assure Safe Use (ETASU)
- Implementation System

The generic REMS has to be the same/comparable to the REMS for the brand drug.

REMS 101: Elements To Assure Safe Use (ETASU)

Depending on the risk, A REMS may require any or all of the following:

- Prescribers have specific training/experience or special certifications
- Pharmacies, practitioners or healthcare settings that dispense the drug be specially certified
- Drug be dispensed only in certain healthcare settings (e.g., infusion settings, 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

REMS 101: Elements To Assure Safe Use

FDA understands that ETASU should not unduly burden patients, healthcare professionals or the healthcare system.

The following provisions help ensure REMS are as efficient as possible:

- ETASU requirements must be commensurate with the specific serious risk listed in the drug's labeling.
- ETASU requirements cannot be unduly burdensome on patient access to the drug.
- To the extent practicable, ETASU must conform with other components for other drugs with similar serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

Examples: REMS with ETASU

Caprelsa (vandetanib): drug to treat medullary thyroid cancer

- The intent of the REMS is to educate prescribers and inform patients of the drug's risk of abnormal heart rhythms that can cause sudden death.
- Prescribers must be trained and specially certified.
- Pharmacies must be specially certified.

Tysabri (natalizumab): drug to treat multiple sclerosis and Crohn's disease

- The intent of the REMS is to inform prescribers, infusion center healthcare providers, and patients about the risk for progressive multifocal leukoencephalopathy (PML).
- Prescribers must be specially certified.
- Pharmacies and infusion sites must be specially certified.
- Evidence of documentation of safe-use conditions.

REMS 101: REMS Elements

Timetable for Submission of Assessments

- All REMS for NDAs and BLAs must include a timetable for assessing the effectiveness of their safety measures.

- At a minimum, REMS assessments must be submitted to FDA by 18 months, 3 years, and 7 years after the REMS is approved.

- Assessments can be eliminated after 3 years.

Examples: Information Needed for REMS Assessments

REMS with ETASU may collect data on



Process

- Adherence to REMS requirements/safe use conditions



Utilization

- Demographics of prescribers and patients
- Use in population at risk



Outcomes

- Number/rate of events REMS is attempting to mitigate
- Root Cause Analysis (RCA)

REMS Challenges

- Customization vs. Standardization
- Knowing where the failure in the healthcare system could occur and targeting best interventions to prevent or mitigate the failure
- Often want to change behavior but behavior is influenced by multiple factors and is difficult to observe and assess – so we rely on proxies
- Can track and measure system inputs but associating particular interventions with outcomes will continue to be difficult
- Difficult to determine the appropriate trade off between enhanced safety and additional burden to the health care system
- Lack of sufficient data to determine whether REMS are effective.

REMS Integration Initiative – Background

FDA began an initiative designed to

- evaluate how we have been implementing our REMS authority
- determine how to design REMS that can be better integrated into the existing and evolving healthcare system
- improve future REMS assessments and incorporate the latest methodologies in the evolving science of risk management

In February, HHS Office of the Inspector General report *FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety* affirmed the need to identify and implement reliable methods to assess the effectiveness of REMS and REMS components

REMS Integration Initiative – Background (cont.)

FDA gathered preliminary input from stakeholders, including...

- Public Meetings
 - 2010 to obtain input on issues and challenges associated with the development and implementation of REMS.
 - 2012 to assess how REMS Assessment surveys are working.
- Annual meetings with the Drug Safety and Risk Management Advisory Committee to evaluate the elements to assure safe use (ETASU) for specific drugs
- Various FDA advisory committee discussions about pre- and post- approval REMS with ETASUs

REMS Integration Initiative – Goals

1

Develop guidance on how to apply the statutory criteria to determine when a REMS is required

2

Improve standardization and assessment of REMS

3

Improve integration of REMS into the existing and evolving healthcare system

REMS Integration Initiative – Stakeholder Input

- With stakeholder input, evaluate appropriate ways to better integrate REMS into the existing and evolving healthcare system.
- Use public workshops to gather information on methodologies for assessing
 - Whether a REMS is meeting its goals.
 - The impact of REMS on patient access and burden on the healthcare delivery system.
- FDA seeks information, comments, and experiences from a broad group of stakeholders.

REMS Integration Initiative – Structure

REMS Integration Steering Committee (RISC)
Oversees the activities of 3 workgroups and stakeholder engagement activities

REMS Policy Workgroup

Develop principles for how to apply the statutory criteria to determine whether a REMS is necessary and other issues associated with requiring or releasing 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.

REMS Integration Initiative – Stakeholder Outreach

The REMS Integration Initiative has a multi-faceted approach to soliciting stakeholder input.

Public Meetings and Public Comments

- Standardization
- Evaluation
- Advisory Committees
- Other

Stakeholder Listening Sessions

- Patients
- Health Professionals
- Prescribers
- Pharmacists
- Pharmacy Systems

Expert Panels

Topics to be determined (e.g. FMEA)

PDUFA Performance Goal

PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017

...XI. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

User fees will provide support for 1) enhancing risk evaluation and mitigation strategies (REMS) by measuring their effectiveness and evaluating with stakeholder input appropriate ways to better integrate them into the existing and evolving healthcare system...

PDUFA Commitments

PDUFA Commitment	Expected Completion Date	
	2013	2014
Guidance	September 30 Publish guidance on how to apply statutory criteria to determine when a REMS is needed	September 30 Publish guidance on methodologies for assessing REMS
Public Meetings	September 30 Hold one or more public meetings to explore strategies for standardizing REMS to reduce burden on health care system September 30 Hold one or more public workshops on methodologies for assessing REMS	
Reports	December 31 Publish a report of findings that will identify 4 priority projects for pharmacy systems, prescriber education, providing benefit/risk information to patients, and practice settings.	

Policy Work Group – Immediate Goals

1

Fulfill the PDUFA V Commitment to develop and issue guidance on how FDA applies the statutory criteria to determine whether a REMS will be necessary to ensure that the benefits of a drug outweigh the risks.

2

Incorporate the considerations and factors utilized in current benefit-risk assessments to maximize the consistency in decision-making about the need for and components of REMS.

3

Address how to proceed when a serious risk

- is not mitigable (cannot be mitigated)
- is mitigable but FDA could approve the drug without a REMS

Policy Work Group – Stakeholder Input

FDA has substantial interest in stakeholder input on:

- The important characteristics of a drug's serious risk(s) that would suggest that product labeling is insufficient to manage the risk(s).
- The specific aspects of the healthcare delivery system that indicate that certain REMS elements and/or tools are unnecessary or otherwise redundant.
- The amount and type of serious drug risks patients are willing to accept and under what circumstances, and how this should be factored into decisions about REMS.

Policy Work Group – Draft Guidance

Guidance for Industry
[title]

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) _____ 301-____-____, or (CBER) _____ at 301-____-____ [others?].

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

[[Date]]
[Category]

Purpose of the Guidance is to outline the key factors considered when determining the need for a REMS, and how the factors influence decisions about whether or not a REMS is necessary.

Will reflect:

- Previous public input gathered at July 2010 Public Meeting, from docket comments, and at Advisory Committee meetings
- FDA experience implementing REMS

Additional public input will be obtained after draft guidance issues and is available for comment.

Standardization Work Group – Goals

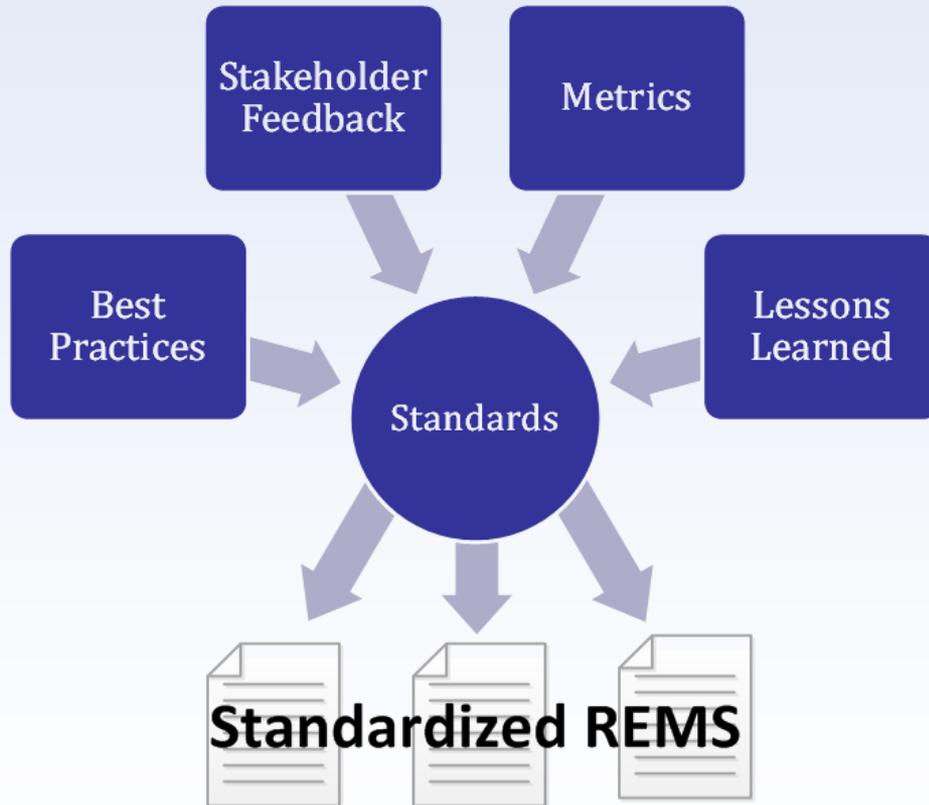
1 Develop a consistent and analytically rigorous approach to the design of REMS.

2 Eliminate unnecessary variation between REMS programs

3 Codify “best practices” to make REMS...

- Less burdensome
- Better integrated into the healthcare system
- More effective
- Easier to assess
- More helpful to stakeholders

Standardization Improves REMS Quality



- Standardization leads to REMS that:
 - Follow best practices from previous REMS
 - Reflect stakeholder feedback
 - Use common metrics

Standardization Work Group – Stakeholder Input

FDA has substantial interest in stakeholder input on:

- Evidence-based program design methods like Failure Modes and Effects Analysis (FMEA)
- Standardizing approaches to mitigating specific types of risks
- Ways to develop and share standardized REMS tools
- Identifying best practices in risk management from across the healthcare system
- Leveraging risk controls already in place in practice settings and healthcare systems
- Impact of technological changes on the horizon
- Standardizing data collection and monitoring to improve REMS evaluation

Standardization Work Group – Key Challenges

Developing standardized approaches to...

- Characterizing and evaluating risks
- Mitigating specific risks or types of risk
 - that do/do not lend themselves to a standardized approach
 - while allowing the flexibility necessary to accommodate diverse healthcare settings

Developing standardized tools and materials that can be used across a variety of REMS

- Advantages, disadvantages, and barriers to development
- Responsibilities for developing and maintaining a standardized set of REMS tools and materials

Standardization Work Group – PDUFA Deliverables



Public Meeting

By September 30, 2013:
Hold public meeting(s) on REMS
standardization



By the end of 2013:
Issue a report of our findings that will
identify priority projects for pharmacy
systems, prescriber education, providing
benefit/risk information to patients, and
practice settings.

Evaluation Work Group – Goals

1

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

2

Develop a REMS Assessment Framework in line with PDUFA V directive to enhance REMS by measuring their effectiveness and burden.

Evaluation Work Group – Preliminary Framework

- Facilitates identifying and resolving gaps in how REMS performance has been measured to date
- Defines metrics and measurement systems for all relevant assessment domains
- Enables Sponsors to define performance metrics based on REMS program intent (e.g. educate, change behavior, etc.) and the targeted stakeholder(s)
- Serves as a blueprint for developing future draft guidance

Evaluation Work Group – Stakeholder Input

FDA has substantial interest in stakeholder input on:

- Setting appropriate goals/objectives and performance levels for the REMS
- Assessing not only knowledge and compliance, but also behaviors, outcomes and access/burden
- Existing and new metrics and measurement systems assessing performance and improvements
 - Behaviors
 - Outcomes
 - Burden/access
- Informing how REMS may need to be modified
 - Root causes
 - Success of a REMS
 - Benefit-risk-burden profile

Evaluation Work Group – PDUFA Deliverables



Public Meeting

By September 30, 2013:
Hold public meeting on additional evaluation methodologies for assessing the effectiveness and impact of REMS, including the effect on patient access, individual practitioners, and burden on the healthcare delivery system.



By September 30, 2014:
Issue Draft Guidance on methodologies for assessing whether a REMS with ETASU

- Assures safe use of the drug
- Is commensurate with the serious risk in labeling
- Is not unduly burdensome to patient access to the drug

Planned Stakeholder Engagement Activities 2013

March 2, 2013	APhA REMS Roundtable
March 8, 2013	PDUFA Stakeholders Meeting to update on the progress of the REMS Integration Initiative.
March – June 2013	Stakeholder Listening Sessions—Experience Implementing ETASU REMS
Summer 2013	Standardization and Evaluation Public Meeting
Summer 2013	DSaRM Advisory Committee Meeting
Late Summer/ Autumn 2013	Expert Panel Meeting (FMEA)

Summary

The FDA Amendments Act (2007) authorizes FDA to require REMS (risk evaluation and mitigation strategy).

REMS are required risk management plans that use risk mitigation strategies beyond professional labeling to ensure that the benefits of prescription drugs outweigh their risks.

FDA created the REMS Integration Initiative, designed to evaluate and improve our implementation of REMS authorities.

The REMS Integration Initiative incorporates input from stakeholders on issues and challenges associated with the development, implementation and assessment of REMS.