FDA Public Meeting

Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)

July 25, 2013

Opening Remarks

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Housekeeping

- Turn off cell phones or set to vibrate/silent.
- All attendees sign in on both days.
- Restrooms left and right hallways.
- 15 minute morning and afternoon break each day.
- Lunch break each day 55/60min.
- Sandwiches, salads, snacks, and beverages available for purchase in the lobby.
- WiFi access code = guestaccess
- 2 Open Public Comment Sessions on Friday (45/60 min). Sign up at the desk.
- Docket for written comments will remain open indefinitely. Submit comments **no later than September 16th** to be considered for FDA's report of its findings on standardization and identification of priority projects.
- Transcript available in +/-60 days on meeting website. http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm351029.htm

Meeting: Overview

- Purpose
- Format
- Agenda

Meeting: Purpose

1. Obtain feedback from stakeholders on:
   - Issues and challenges associated with standardizing and assessing REMS for drug and biological products
   - Identifying potential projects that that will help standardize REMS and integrate them into the health care delivery system
2. Meet performance goals included in the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA).

Meeting: Format

- **FDA Presenters** will introduce the topics for the panel sessions and highlight some information included in the background document. http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm358784.htm
- **Stakeholder Panels** will provide input on the questions listed in the Federal Register Notice. Panels have been organized based on outlines submitted in advance of the meeting.
- **FDA Panel**, representing a subset of many people at FDA who are experienced with REMS, will listen and ask questions as time permits.
- **Open Public Session** will provide an opportunity for those who did not register to speak but would like to present some comments, to speak as time permits.

Meeting: Agenda

July 25, 2013

FDA Presentations

- Meeting Overview/REMS Update
- Standardizing REMS
- Prescriber-Directed Tools in REMS
- Patient- Directed Tools in REMS
- Dispensers and Dispensing Settings in REMS

Stakeholder Presentations

- Panel 1 General Standardization Issues
- Panel 2 General Standardization Issues
- Panel 3 Prescriber and Patient Directed Tools in REMS
- Panel 4 REMS Tools Used in Dispensing Settings

July 26, 2013

Stakeholder Presentations

- Panel 5 Standardization Projects

Open Public Hearing: Standardization

FDA Presentations

- REMS Assessments: A Summary of FDA's Experiences and Challenges
- Building a Framework for Future REMS Assessments

Stakeholder Presentations

- Panel 6 General Evaluation Issues

Open Public Hearing: Evaluation

Outline

- **REMS: FDA Update**
  - Background
  - Stakeholder Input
  - Challenges
  - REMS Integration Initiative
    - Workgroups
    - Stakeholder Engagement
- **Summary**

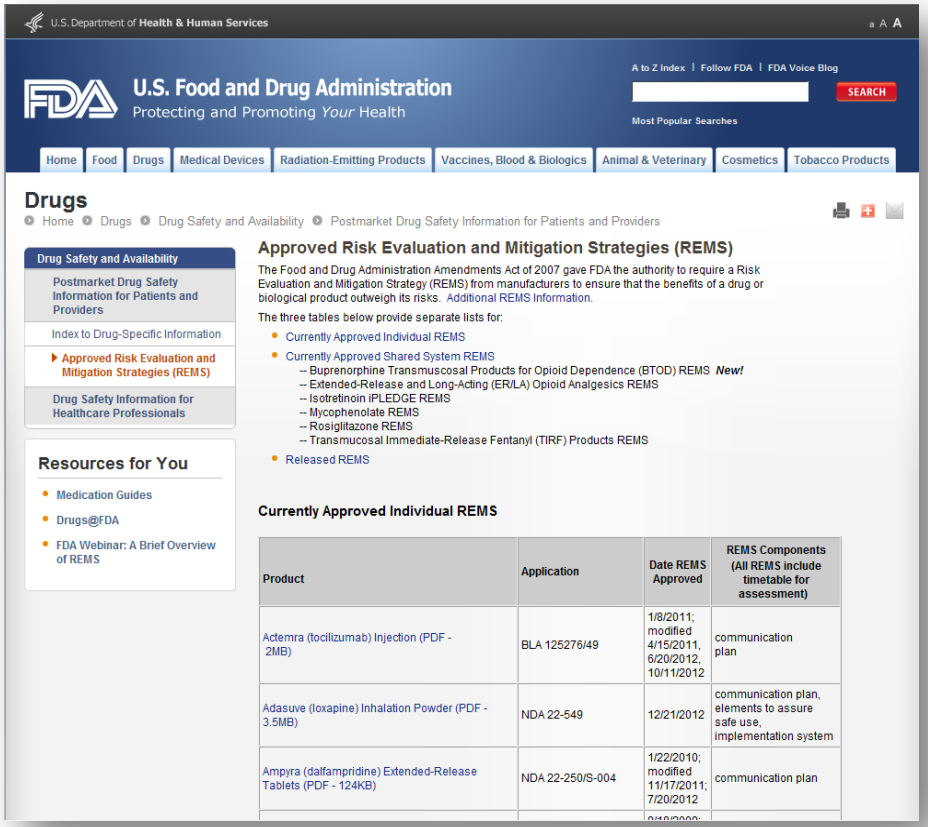
REMS Background

- For the majority of approved products, FDA has determined that labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits.
- 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.

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

Approved REMS



- 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)

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

Listening to Patients and Health Care Providers

"… we hope to make sure that … care providers as well as patients **understand these products so that they remain accessible to the patients for whom they are appropriate."**

"I **like the repetitiveness** that every time I have to talk about my usage. There's **no assumption that I'm doing it right just because I've used it a long time. I think that's a good thing**."

"It is also important to recognize that **while these tools may seem time consuming, they can be incredibly helpful."**

"Am I really doing anything other than just filling out paperwork?"

"But if we start adding 3, 4,5, 6 of these REMS programs and they're all different, different requirements, different websites, this has a much larger **impact on [pharmacy] workflow**."

"We're always afraid of things, but when you try it **– it's like eating your vegetables,** you know, when you try it, it's just a lot easier."

Listening to the Pharmaceutical Industry

"One size does not fit all."

"There are opportunities for standardization, however, … there are **differences between drugs in terms of their benefits, their [risk] potential, and the settings for their use that will justify flexibility within any standardization**."

"Implementation of [a REMS verification system] **may impose new patient access issues**, therefore the decision to use **any REMS verification system requires careful consideration**."

"The uses, benefits, and risks of a drug will change over time, and the risk management system may need to adapt with it, so **some flexibility is warranted."**

"…stakeholders felt that ideally a **REMS should equally balance benefit and risk information."**

"Knowledge assessments are important,… but **in the end we want to know that we changed behavior through risk mitigation**, although that will always be difficult to assess."

Listening to FDA Reviewers

"Companies that actually **do good pre-testing of materials** and react, is such a gift to us."

"One company that does a particularly good job with REMS submissions provides an **accompanying document that provides rationale for every change**. This really helps to **expedite the review process."**

"Something very basic is how sponsors submit documents ... we go back and forth to just get the **documents in the correct format."**

"Many last minute surprises could be avoided if sponsors conceptualized and communicated **how pending labeling changes may affect REMS programs and materials downstream**."

"We need to better **understand the sponsor/vendor processes** to establish best practices for developing and finalizing REMS documents."

"We've learned, and continue to improve upon the **importance of directly linking REMS goals, to elements, to assessments**."

REMS Challenges

- The science and statutory framework for pharmaceutical risk management continues to evolve.
- FDA continues to learn more about various aspects of REMS, including
  - making decisions about the need for REMS
  - designing REMS programs that can be readily implemented and integrated into the existing healthcare system
  - measuring REMS effectiveness
  - minimizing the burden on patient access and the health care system.
- Lessons learned highlight challenges and opportunities associated with REMS policy, standardization, integration and evaluation.

Some REMS Challenges: Policy

- When may an alternative to REMS be appropriate to address a serious risk?
- What are indicators that
  - product labeling is insufficient to communicate the drug's risks and conditions of safe use?
  - a REMS is no longer necessary to ensure the benefits of a drug outweigh the risks?

Some REMS Challenges: Design/Standardization

- How to best balance customization and standardization?
- How much variation is necessary and unavoidable?
- How to target best interventions to prevent or mitigate failures?
- What is the appropriate trade off between enhanced safety and additional burden to the health care system?

Some REMS Challenges: Assessment

- What are valid proxy measures of patient and provider behavior to determine if REMS goals have been met?
- How to associate particular REMS interventions with specific outcomes?
- How to use limited data to determine whether REMS are effective?

REMS Opportunities

- In 2011, FDA established the REMS Integration Initiative designed to
  - Review how we have been implementing our REMS authority
  - Define policy for requiring a REMS
  - 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
- FDA has been gathering input from stakeholders through a variety of stakeholder engagement activities.

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.

REMS Policy Workgroup

- Developing a draft guidance
  - How to apply the statutory criteria to determine whether a REMS is necessary to ensure that the benefits of a drug outweigh the risks.
  - Describe considerations FDA takes into account in current benefit-risk assessments of drugs to maximize the Agency's consistency in decision-making about the need for REMS.
  - Provide information about when it may be appropriate to employ measures other than a REMS to address a serious risk.

REMS Design and Standardization Workgroup

- Identifying
  - best practices to incorporate into REMS design
  - ways to standardize REMS tools and integrate REMS into the healthcare delivery system
  - ways to eliminate unnecessary variation in REMS
- Soliciting stakeholder input on
  - best practices in risk management from across the healthcare system
  - evidence-based program design methods like Failure Modes and Effects Analysis (FMEA)
- Publishing a report of findings to include identification of projects that will help standardize REMS and integrate them into the health care delivery system

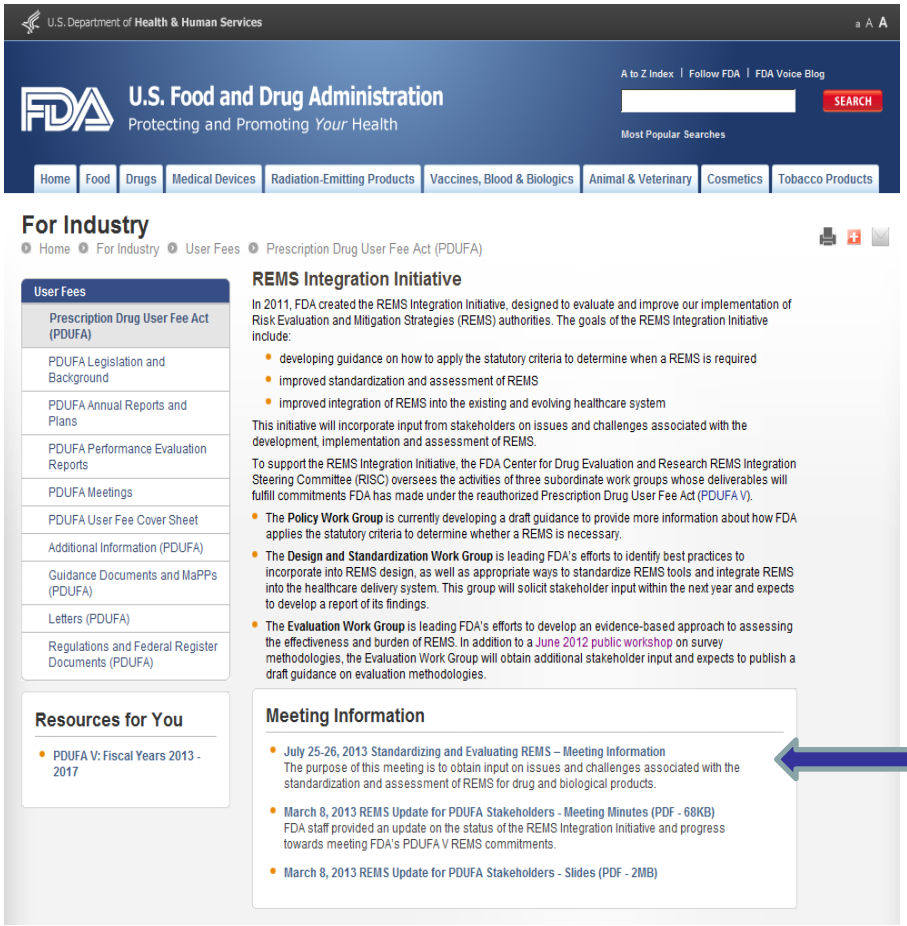
REMS Evaluation Workgroup

- Developing an evidence-based approach, including a REMS Assessment Framework, to measure the effectiveness and burden of REMS
- Soliciting stakeholder input on
  - ways to set appropriate goals/objectives and performance levels for the REMS appropriate metrics and measurement systems
  - assessing performance and improvements for behaviors, outcomes, burden and access
- Publishing a draft guidance on evaluation methodologies

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	15 Stakeholder Listening Sessions—Experience Implementing ETASU REMS
May 16, 2013	Drug Safety Board Meeting
May 23, 2013	Trends Emerging in Risk Management (TERM) Meeting
July 10, 2013	DSaRM Advisory Committee Meeting
July 23, 2013	Council of Medical Specialties Meeting
July 25-26, 2013	Standardization and Evaluation Public Meeting
Autumn 2013	Expert Panel Meeting (currently considering FMEA and Assessment Framework)

REMS Integration Initiative – Comments



Submit electronic comments to *http:// www.regulations.gov.*

Submit written comments to Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm.1061
Rockville, MD 20852

Identify each set of comments with the corresponding docket number for the public meeting as follows:
Docket No.FDA–2013–N–0502.

Docket for written comments will remain open indefinitely. Submit comments no later than **September 16th** to be considered for FDA's report of its findings on standardization and identification of priority projects.

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM350852

Summary

- FDA has regularly sought stakeholder feedback to understand how existing REMS programs are working and where opportunities for improvement exist.
- FDA created the REMS Integration Initiative to facilitate:
  - developing guidance on how to apply statutory criteria to determine when a REMS is required
  - improving standardization and assessment of REMS
  - improving integration of REMS into the existing and evolving healthcare system.
- FDA looks forward to today's meeting to hear more from stakeholders about
  - challenges with and opportunities for standardizing and assessing REMS.
  - potential projects that will help standardize REMS and integrate them into the health care delivery system.

Standardizing REMS

Adam Kroetsch
Operations Research Analyst
Office of Program and Strategic Analysis

Overview

1. Introduction to REMS Standardization
   - What we are standardizing
   - Why we are standardizing

2. Steps toward Standardization
   - Characterize Existing REMS
   - Identify Best Practices
   - Standardize REMS

FDA has committed to standardizing and integrating REMS

Under its PDUFA V commitments, FDA has agreed to standardize REMS and better integrate them into the existing and evolving healthcare system.

- Hold public meeting(s) on REMS standardization with the goal of reducing REMS burden.
- Issue a report of our findings.
  - Report will identify priority projects in several areas.

What are we standardizing?

REMS Design: How REMS tools are selected

- REMS design begins once we know about the risk and what is required to mitigate it
- Includes standardized methods to:
  - Characterize how the drug is likely to be used
  - Identify "gaps" in the healthcare system that lead to greater risk
  - Determine REMS "safe use conditions" to address gaps
  - Select appropriate REMS tools

What are we standardizing?

REMS Tools: Systems/processes to carry out the REMS "safe use conditions".

- Includes standardizing:
  - What tools are used (e.g., a REMS "toolkit")
  - How those tools are implemented and integrated into the healthcare system.
  - The means by which the tools are assessed

REMS tools are a major focus of this meeting.

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Why have REMS varied?

1. Risks vary.
   - REMS are designed to address specific serious risks, and the steps needed to mitigate these risks will vary.

2. The context of care varies.
   - Different REMS drugs are used by different providers in different healthcare settings for different patient populations.

Why have REMS varied?

3. The "developers" of REMS vary
   - REMS are proposed by a diverse set of sponsors and negotiated with FDA review teams.

4. Best practices are still evolving
   - The science of pharmaceutical risk mitigation is comparatively new and REMS "best practices" are still being developed.

Stakeholder feedback highlights need to address variation

- Variation makes it difficult to adapt to new REMS
  - Even stakeholders with significant REMS experience can take time to integrate new REMS into their workflow.
  - Stakeholders don't always understand what they need to do to implement new REMS.
- REMS successes aren't always copied.
  - Some stakeholders had "favorite" REMS or REMS tools, but these successes weren't necessarily repeated
- Healthcare providers' perceptions of REMS varied greatly depending on their setting

Standardization should lead to consistent, high-quality REMS

To address stakeholder concerns, we seek to…

- Minimize unnecessary variation: Make REMS more consistent, predictable, and easier to understand, but customize REMS to specific settings.
- Improve quality: Establish "best practices" that make REMS more effective, less burdensome, and maintain patient access.

What Standardization Looks Like

	Minimize Variation	Improve Quality
REMS Design	**REMS that address similar risks with similar stakeholders / settings use similar tools**	**Rigorous and evidence-based approaches are used to set REMS goals and requirements**
REMS Tools	**REMS use similar tools drawn from a standardized REMS "toolkit".**	**REMS tools are informed by the latest science, stakeholder feedback, and established "best practices".**

Overview

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   - What we are standardizing
   - Why we are standardizing

2. **Steps toward Standardization**
   - Characterize Existing REMS
   - Identify Best Practices
   - Standardize REMS

Steps toward Standardization

1) Characterize Existing REMS

- Catalog current REMS
- Improve how REMS information is captured and shared

2) Identify Best Practices

- Get feedback from internal and external stakeholders and experts*
- Identify priority projects*

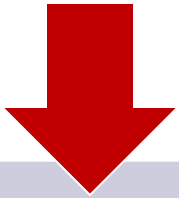
3) Standardize

- Complete priority projects
- Share findings
- Develop/Update guidance

* These activities are part of FDA's PDUFA V commitments

Steps toward Standardization

We are here



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Steps toward Standardization

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REMS often lack common definitions and clear requirements

- The format of REMS documents/materials varies
- REMS lack consistent terminology
  - Similar tools often have different names
  - Different tools often have the *same* name
- Regulatory terms like “ETASU”, “Communication Plan” and “ETASU A-F” do not provide useful information about how REMS programs work.
- It’s not always easy to find information on what is expected of healthcare providers and patients.

Unclear definitions make standardization difficult

Example: Patient/Prescriber Agreement and Enrollment Forms

REMS	Form Name	Patient Agreement	Prescriber Agreement	Patient Enrollment
ESAs	Patient and Healthcare Professional Acknowledgment Form	✓	✓	
Isotretinoin	Patient Information / Informed Consent	✓	✓	
Rosiglitazone	Patient Enrollment Form	✓	✓	✓
Lotronex	Patient Acknowledgment Form	✓		
Thalomid	Patient-Physician Agreement Form	✓	✓	✓

We are working to better describe how REMS vary

- Before we can standardize REMS, we need a "common language" to describe REMS variation.
- We have cataloged and characterized existing REMS documents and materials, including:
  - The text of the REMS document
  - Information about REMS materials (e.g., training)
  - Information about specific REMS requirements (e.g., need for certification)

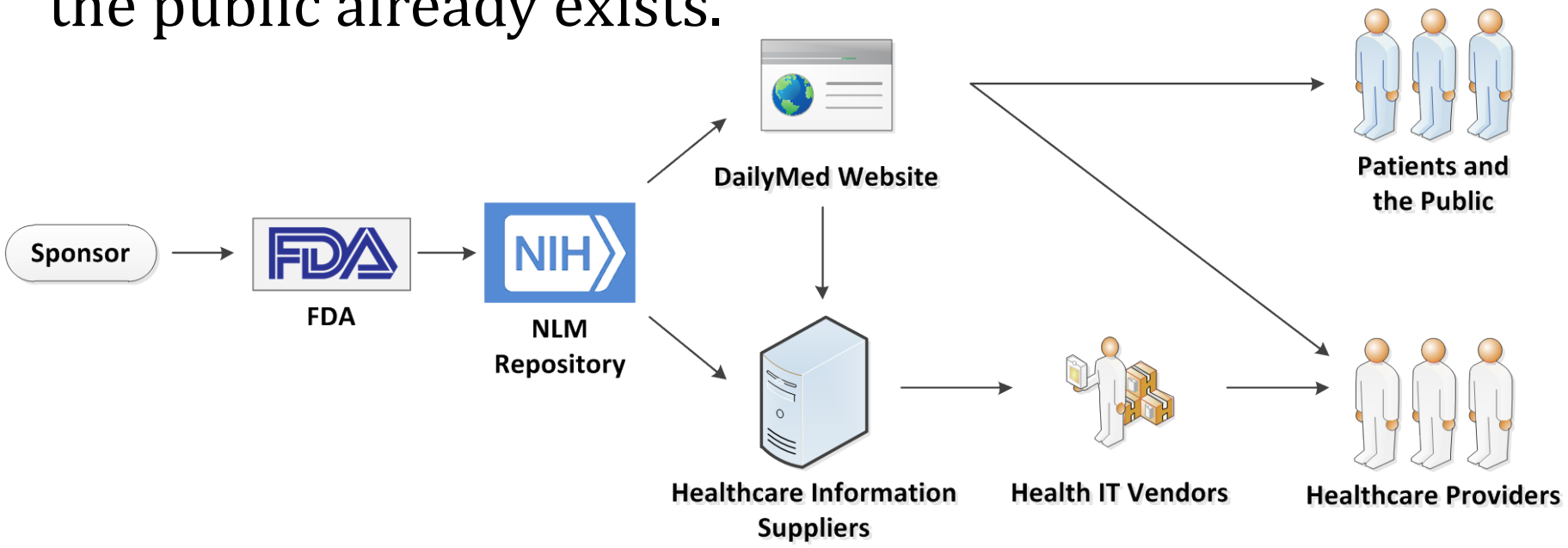
Initial findings from this effort informed the public meeting background materials

SPL can improve how REMS information is captured and shared

- To better characterize and share information about REMS, FDA seeks to include REMS information in "Structured Product Labeling" (SPL)
  - SPL is a broadly-used standard to capture structured information about drugs and their labels.
  - SPL is developed with the help of stakeholders.
  - SPL can include both documents (e.g., the REMS document) and structured, machine-readable information (e.g., information to support electronic health records)

SPL information is shared across the healthcare system

The infrastructure to transmit information from the sponsor to patients, healthcare providers, and the public already exists.



SPL can help promote the development of standardized REMS

- Makes it easier to develop consistent REMS documents
  - Through SPL, the desired format of REMS documents can be clearly defined.
- Facilitates efficient review of those documents
  - Can automatically check for standardized format
- Supports future standardization efforts
  - Makes it simpler to track how different REMS tools are being used and where greater standardization may be needed.

SPL can also make it easier for stakeholders to implement REMS

- Helps clarify what the REMS requires of patients and healthcare providers
  - SPL can consistently describe REMS requirements
- Puts relevant REMS information in one place:
  - Makes REMS materials readily available online
  - Makes it easier to build "REMS portals" with information about a range of REMS.
- Allows REMS information/requirements to be incorporated into EHRs, ePrescribing, and pharmacy systems.

Steps toward Standardization

1) Characterize Existing REMS

- Catalog current REMS
- Improve how REMS information is captured and shared

2) Identify Best Practices

- **Get feedback from internal and external stakeholders and experts***
- **Identify priority projects***

3) Standardize

- Complete priority projects
- Share findings
- Develop/Update guidance

*** These activities are part of FDA's PDUFA V commitments**

FDA will reach out to stakeholders

FDA is seeking stakeholder and expert feedback

- Ways to help build more effective and better-integrated REMS tools
  - This is one of the primary goals of today's meeting
- Methods to assess and characterize risks and select appropriate REMS tools or interventions (e.g., Failure Mode and Effects Analysis)
  - To explore this area further, we will be holding an expert workshop this Fall.

We are seeking feedback on specific REMS Tools

- Prescriber-directed tools
  - Training: What are the best ways to educate and train prescribers? (and other healthcare providers)
  - Certification / Enrollment: How can we streamline enrollment?
- Patient-directed tools
  - Education: What are the most effective and efficient ways to educate given the variety of information needs and learning styles?
  - Counseling: How can we improve patient counseling?

We are seeking feedback on specific REMS Tools

- Tools in dispensing settings:
  - Certification / Enrollment: How do we manage certification of dispensers, given the wide variety of dispensing settings in REMS?
  - Distribution controls: How can we make REMS compatible with established systems for procurement, distribution and dispensing?

The next three presentations will focus on these questions.

FDA is also seeking help identifying priority projects

- Priority projects could help identify or test new ways to standardize and integrate REMS.
- PDUFA V identified four project areas:
  - Educating Prescribers
  - Providing Benefit-Risk Information to Patients
  - Pharmacy Systems
  - Practice Settings
- Under PDUFA V, we have committed to developing a workplan for completion of each project.
  - Workplan will be part of report following this meeting.

Steps toward Standardization

1) Characterize Existing REMS

- Catalog current REMS
- Improve how REMS information is captured and shared

2) Identify Best Practices

- Get feedback from internal and external stakeholders and experts*
- Identify priority projects*

3) Standardize

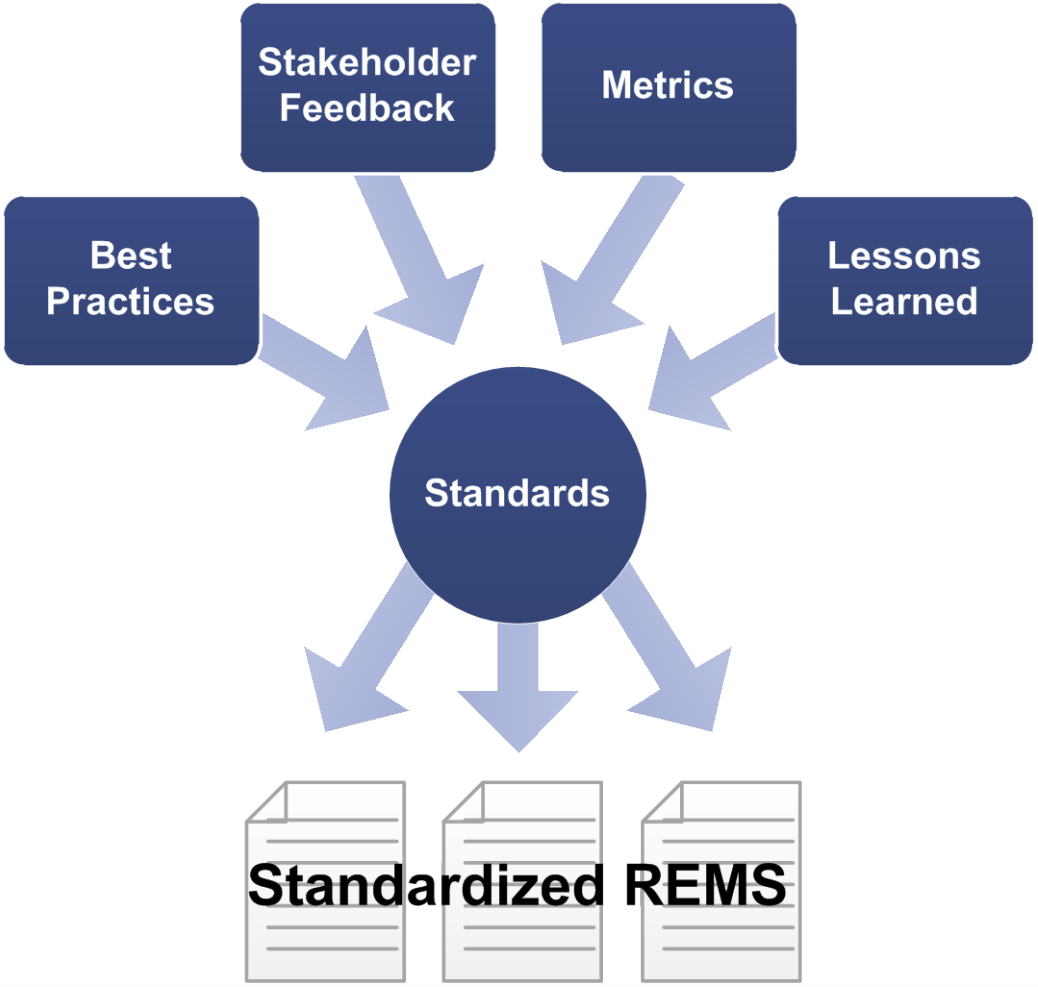
- **Complete priority projects**
- **Share findings**
- **Develop/Update guidance**

* These activities are part of FDA's PDUFA V commitments

As we standardize, we will follow certain principles

- Listen to stakeholders.
  - Work collaboratively with patients, practitioners, industry, and outside experts to identify best practices.
- Build evaluation into standards.
  - Ensure that goals, programs, and tools are aligned and measurable to provide evidence on whether they work .
- Work iteratively.
  - Allow standards to evolve over time as we learn more.
- Be flexible.
  - Encourage new and innovative approaches.

Standardization facilitates continuous improvement of REMS



Standardization leads to REMS that:

- Use best practices
- Incorporate stakeholder feedback
- Build in evaluation
- Build from lessons learned in previous REMS

Prescriber-Directed Tools in REMS

Kate Heinrich Oswell, MA
Health Communications Analyst
Division of Risk Management
Center for Drug Evaluation and Research

Objectives

- Provide an overview of prescriber-directed tools used in REMS
- Share feedback from stakeholders about prescriber-directed tools
- Share some “promising practices”

Overview

REMS programs use a number of tools to:

- Educate healthcare providers
- Ensure that healthcare providers carry out REMS requirements including screening, monitoring, and counseling patients

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

Stakeholder Feedback

- Offer different options for training
- Standardize enrollment forms
- Streamline process
  - 'One stop' website for all REMS programs
  - Patient enrollment through REMS website at physician office

Some Promising Practices

- CE credit for REMS training
- Checklists and quick summaries
- Single web portal for similar programs

Patient-Directed Tools in REMS

Ana Tavakoli, MA
Health Communications Analyst
Division of Risk Management
Center for Drug Evaluation and Research

Objectives

- Provide an overview of patient-directed tools used in REMS
- Share feedback from stakeholders about patient-directed tools
- Highlight the importance of consumer testing materials prior to dissemination

Overview

REMS programs use a number of tools to:

- Educate and counsel patients
- Provide patients with information about the risks of the drug
- Help to ensure that patients use the drug safely

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

Stakeholder Feedback

- Repeated counseling can be beneficial
- Create "Straightforward patient counseling documents" such as checklists
- Offer a variety of tools including both print materials and digital media
- Create materials that are patient-friendly and written at a an appropriate reading level

Consumer Testing of Materials

The Agency has seen modifications submitted by sponsors based on consumer-testing of REMS materials that have shown improvements in them.

- REMS materials tested:
  - Patient-Provider Agreement Form
  - REMS-dedicated website

Consumer Testing Materials

Findings:

- Forms should be formatted for easier readability and understandability
- Risks and benefits of drug should be clearly defined in materials
- Materials should include content that are written using plain language principles

Improvements can often be made when materials are pre-tested with patients prior to dissemination. Therefore, we encourage all sponsors, to test their materials prior to submitting them for review.

Dispensers and Dispensing Settings in REMS

Megan Moncur, M.S.
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Division of Risk Management
FDA/CDER/OSE/OMEPRM

Objectives

- Provide an overview of dispensers and dispensing settings in REMS
- Share some example feedback from dispensers
- Share some "promising practices"

Drugs are Dispensed in a Wide Range of Settings, for Example:

- Retail pharmacy
- Hospital
- Prescriber's office
- Infusion center
- Office-based surgery center
- Behavioral health treatment facility
- Specialty pharmacy

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 an "Authorized Party"
- Train and/or ensure staff are trained
- Enroll
- Establish tracking and/or document management systems
- Modify existing systems and/or processes (electronic and/or manual)

REMS Requirements for Dispensers (2)

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

- Verify 'documentation of safe-use conditions'
  - Record that verification occurred
  - 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

Dispensing Setting Dimensions of Variation

- Role in the patient care process
- Existing "safe-use controls"
- Existing electronic health systems
- Corporate or organizational structure
- Integrated/closed healthcare system
- Procurement process
- Transitions of care

Example Feedback from Dispensers

- REMS need to clearly and concisely convey what dispensers are required to do
- REMS processes should be automated and integrated into the workflow
- REMS requirements should be customized to different dispensing settings
- Want flexibility in how the REMS requirements are implemented

Some Promising Practices

- Integration into existing systems and workflow
  - Inpatient order sets
  - Outpatient pharmacy management system/claims process used to verify documentation of safe-use conditions
  - REMS forms adapted to be compatible with existing health systems
- Setting-specific customization
  - Several REMS have different requirements for outpatient and inpatient pharmacies
  - Custom process for closed/integrated systems
  - Outpatient pharmacy enrollment forms customized for independent, chain, and closed system pharmacies

Building a Framework for Future REMS Assessments

REMS Standardization and Evaluation Public Meeting

July 26, 2013

Gary Slatko, MD

Director

Office of Medication Error Prevention and Risk Management

CDER/FDA

Agenda

BACKGROUND

APPROACH

FACTORS AND PRINCIPLES

EXAMPLE FRAMEWORK

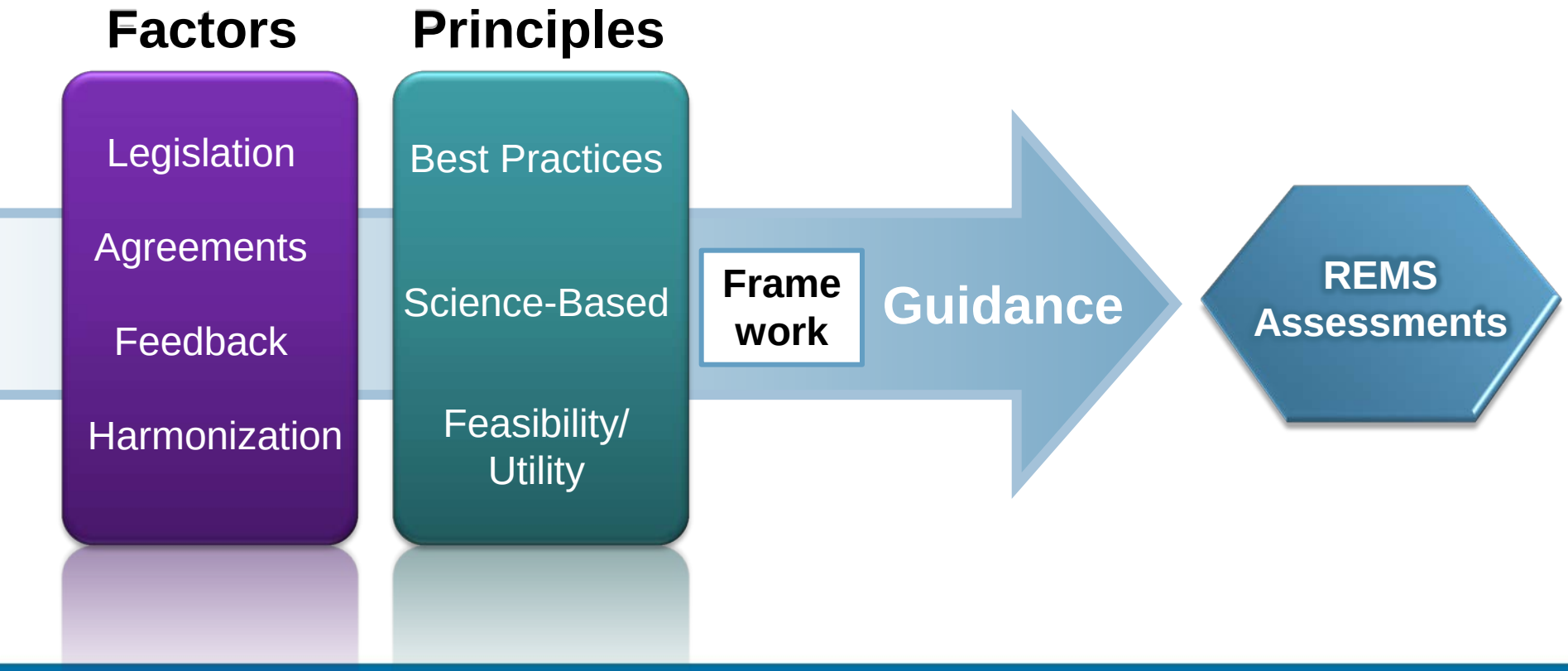
VALUE

CONCLUSION

Background

- Historically, REMS assessments have had limitations and “lacked clarity”
  - Limitations of methods used e.g., surveys
  - Focused on a subset of available “domains”
  - Variability across programs
  - Limited utility of results for decision making

Evolving Guidance for a More Standardized and Robust REMS Assessment Methodology: Overview of Approach



Legislation

FACTORS

- FDAAA (2007) requires that assessments be done to determine if a REMS is meeting its goals
- FDASIA (2012) impacts the scope of REMS assessments by
  - authorizing PDUFA V and related agreements
  - highlights the need to consider benefits and burden on the healthcare system when modifying REMS

Agreements – PDUFA V

FACTORS

Goal (XI.A.3.)*: **Measure the Effectiveness of REMS** and Standardize and Better Integrate REMS into the Healthcare System"

1. One or more public workshops on methodologies for assessing REMS, including effect on patient access, individual practitioners and overall burden on the healthcare delivery system
2. Guidance on methods for determining whether a REMS with ETASU is commensurate with the risks and not unduly burdensome on patient access

Feedback - Industry

- Public Workshop (July, 2012): S
  to Assess Goals Related to Kn
  - Presentation: Industry Experie
    - **Need consensus on key out**
    - Research design issues
    - Special populations
    - Questionnaire design
    - Survey administration
    - Survey results and interpretation
  - **Additional data collection options**
  - Need to apply "best design p

FACTORS

- **Exposure**
- **Usefulne**
- **Navigability**
- **Comprehension**
- **Knowledge**
  - **Recognition vs. self-generating**
  - **Functional (applied) understanding**
- **Self-efficacy**
- **Behavioral intent**
- **Actual behavior**

- **Drug utilization studies**
- **Patient registries**
- **Secondary data sources**
- **Patient web-based communities**

Feedback - Inspection

FACTORS

- OIG Report (January, 2013): "FDA Lacks Comprehensive Data to Determine Whether REMS Improve Drug Safety" recommendations
  - **Develop and implement a plan to identify, develop, validate and assess REMS components**
  - Identify REMS th… actions to pr…
  - Evaluate the …
  - Identify incomp… obtain missing …
  - Clarify expecta…
  - Seek legislative …
  - Ensure that ass…

- "FDA should also identify and implement reliable methods to **assess the effectiveness of REMS**.
- "FDA should **decrease its reliance on survey data** in sponsors' assessments and work with sponsors and health care providers to **develop more accurate evaluation methods**."
- "Additionally, FDA should continue to hold discussions with stakeholders…about the issues and challenges associated with **assessing the effectiveness of REMS components**."

Feedback - Stakeholders

FACTORS

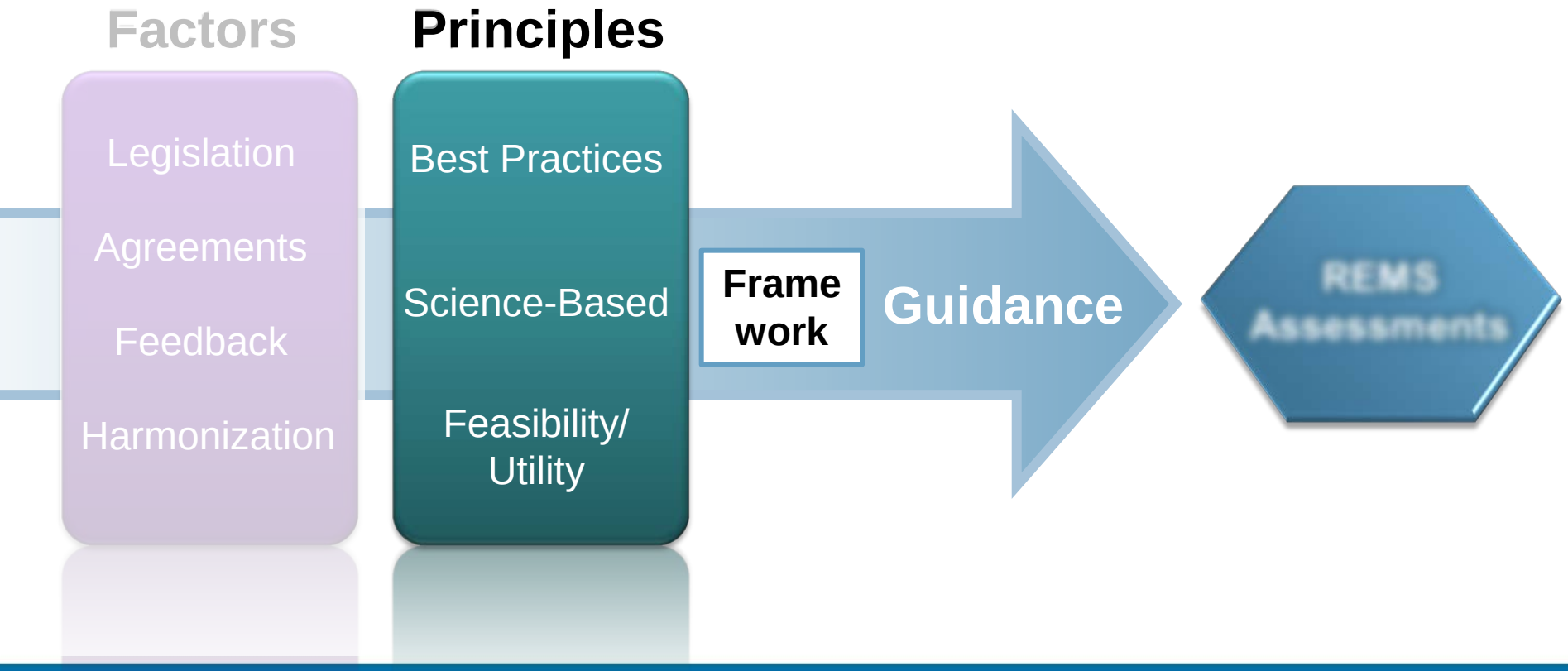
- Feedback has been solicited from various stakeholders about their experience with implementing REMS programs to date
- REMS Standardization and Evaluation Public Meeting: July 25-26, 2013 Silver Spring, MD
  - > 30 Presenters
  - Comment to docket

Harmonization

FACTORS

- EMA Guideline on Good PV Practices (GPV) Module XVI (Draft); Section B.4*
  - Evaluate tools individually and program as a whole
  - Address the (implementation) **process, knowledge, behavior and outcome**
    - Process indicators – extent program has been executed and intended impacts on behavior achieved
      - Reaching target population
      - Assessing clinical knowledge
      - Assessing clinical actions (drug utillization studies)
    - Outcome indicators – measure of level of risk control
      - Frequency and severity (pre-post or observed vs. expected epidemiology studies)
  - Assess unintended consequences

Evolving Guidance for a More Standardized and Robust REMS Assessment Methodology



Maintain Best Practices

PRINCIPLES

- REMS assessments have focused on measuring
  - Implementation **process** metrics (e.g., number of Dear HCP letters distributed, number of Medication Guides distributed)
  - Patient and/or provider **knowledge** metrics (e.g., average % correct responses to a survey of knowledge of risks)
  - Performance in attaining REMS **goal(s)** (e.g., REMS is(n't) achieving its goal)
  - Degree of **compliance** with ETASU requirements (e.g. number of physicians certified)
- Refinement of these methods has occurred over time
  - Consistency across programs
  - Standardized language

Science-Based Approach

PRINCIPLES

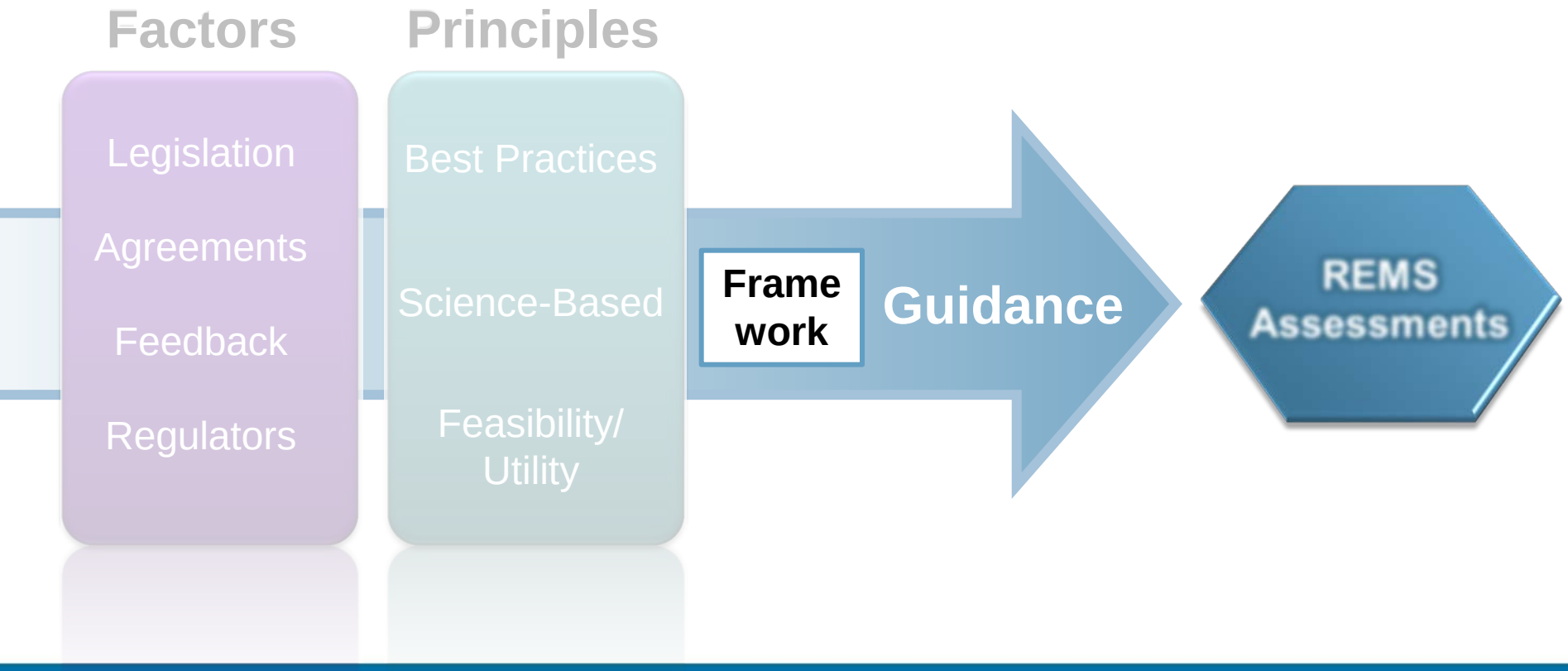
- Consistency with the scientific method
  - Goals and objectives that are measurable
  - Statistically analyzable data
  - Generates information that informs how to improve
- Comparable to pharmacoepidemiology principles and practices
- Comprehensive spectrum of assessment domains
- Grounded in a pre-existing framework that has evidence behind it

Feasibility/Utility

PRINCIPLES

- Any REMS assessment method will have limitations, e.g.,
  - Challenging to do controlled comparative trials
  - Limits to resources/time available to conduct assessments
- Seeking comprehensive, pragmatic and standardizable approach(es) yielding actionable information for making decisions, such as:
  - Causes of tool/program underperformance
  - The types of program modification(s) that may be needed
  - Undesired effects i.e., undue burden, access limits
- Relevance will need to be pre-tested with prior programs

Evolving Guidance for a More Standardized and Robust REMS Assessment Methodology



Framework Options

FRAMEWORK

- Learning process assessment methods
  - Kirkpatrick Four Level Model: reaction, learning, behavior, results
  - Revised Kirkpatrick Model: motivation, learning, performance, results
- Healthcare intervention assessment methods
  - e.g., RE-AIM framework: reach, effectiveness, adoption, implementation, maintenance
- Failure analysis methods
  - Root Cause Analysis (RCA): retrospective analysis of failures and causes
  - Failure Mode and Effects Analysis (FMEA): systematic, prospective analysis of potential failures and causes
- Others?

The RE-AIM Framework

FRAMEWORK

- A well-established framework for assessing healthcare interventions
  - Various disease states
  - Over 15 years of evidence
  - >185 literature citations
- Readily adaptable to the spectrum of assessment information generated from REMS
- May be “best fit”

The RE-AIM Framework

FRAMEWORK

Five Factors:

Factor	Description
Reach	Proportion of the target population who participate
Effectiveness	Success rate (positive – negative outcomes)
Adoption	Proportion of settings that adopt the intervention
Implementation	Extent to which intervention is implemented as intended
Maintenance	Extent to which intervention is sustained over time

Aligning RE-AIM Framework With Potential REMS Assessment Domains (Example)

FRAMEWORK

Category	Possible REMS Assessment Domains	Standardized REMS Metrics for Each Tool
Reach	**Distribution/ availability/ receipt** **Participation** **Medication access**	
Effectiveness	**Knowledge: awareness/ comprehension/ understand** **Outcomes: REMS goal, clinical, patient-reported** **Unintended effects**	
Adoption	**Application of knowledge** **Attitude/ intention** **Behaviors: adoption, actions, compliance**	
Implementation	**Process: pretesting, functionality/navigability, Sponsor, stakeholder workflow, integration** **Consistency** **Burden**	
Maintenance	**Persistency** **Failures**	

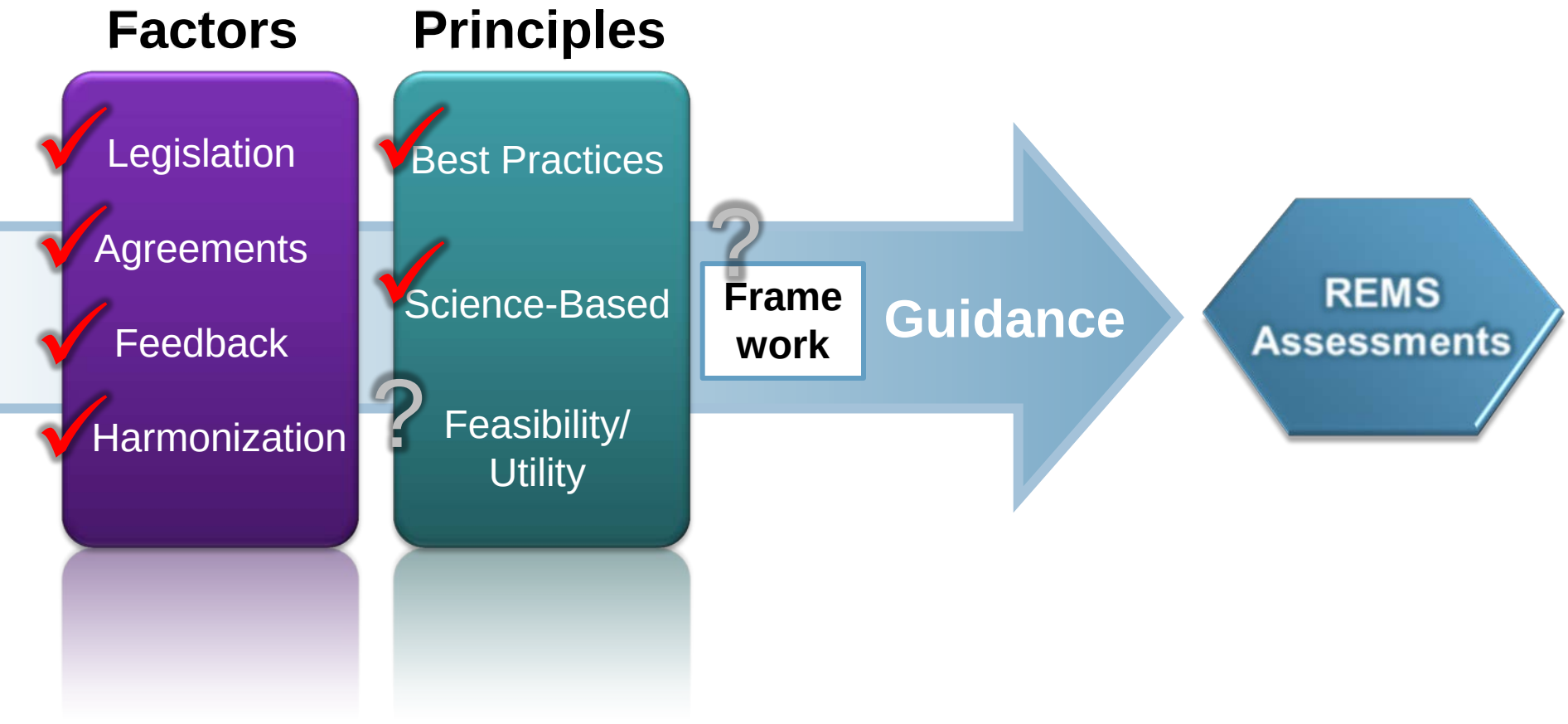
Numerator
Denominator
Data source(s)
Thresholds?

Aligning RE-AIM Framework With Potential REMS Assessment Domains (Example)

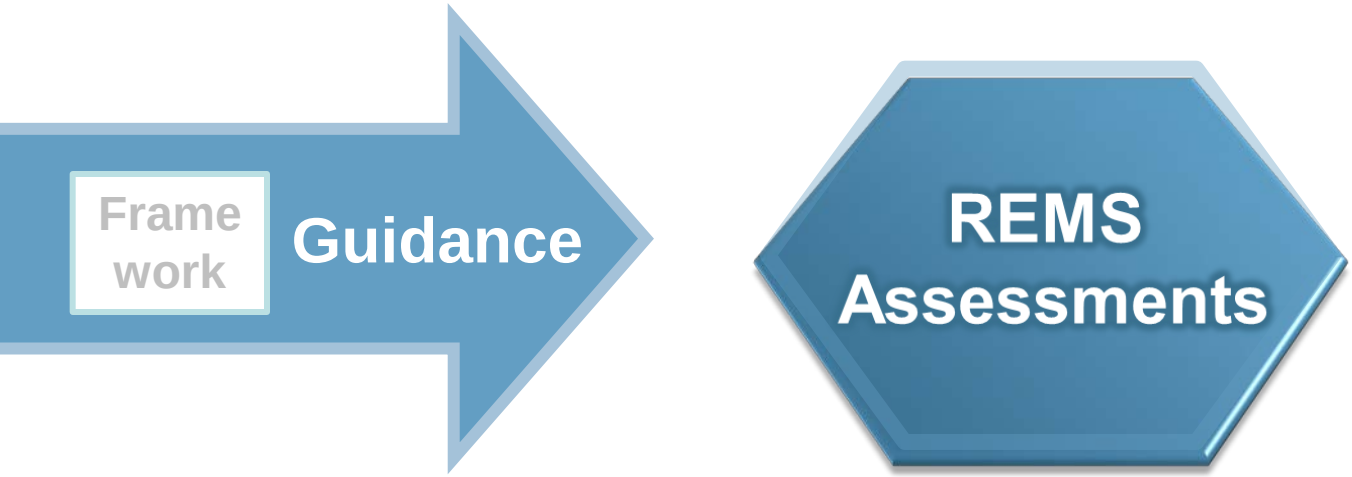
FRAMEWORK

Category	Possible REMS Assessment Domains	Data System/Source
Reach	Distribution/ availability/ receipt Participation Medication access	REMS database Drug utilization studies Patient registries Secondary data Epidemiology studies Surveys Market research Simulation modeling Ethnography FMEA/RCA Audits Enhanced PV PMRs/PMCs Others
Effectiveness	Knowledge: awareness/ comprehension/ understand Outcomes: REMS goal, clinical, patient-reported Unintended effects	
Adoption	Application of knowledge Attitude/ intention Behaviors: adoption, actions, compliance	
Implementation	Processes: pretesting, functionality/navigability, Sponsor, stakeholder workflow, integ. Consistency Burden	
Maintenance	Persistency Failures	

Evolving Guidance for a More Standardized and Robust REMS Assessment Methodology



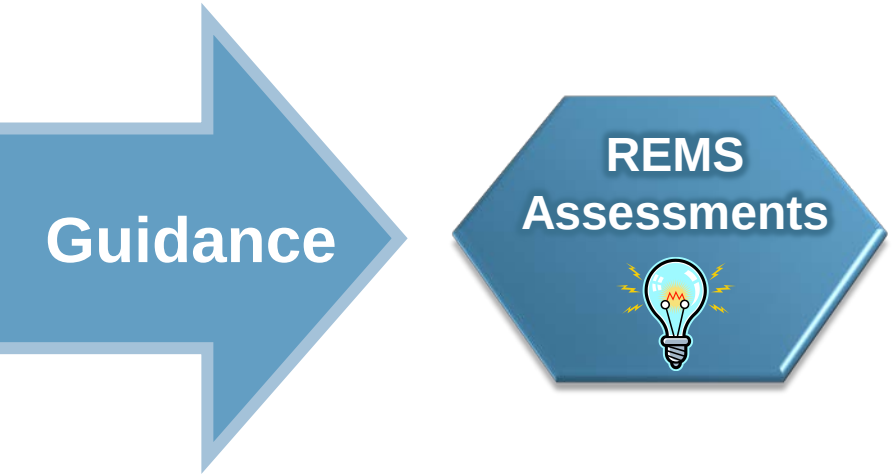
Evolving Guidance for a More Standardized and Robust REMS Assessment Methodology



- ✓ One or more public workshops on methodologies for assessing REMS, including effect on patient access, individual practitioners and overall burden on the healthcare delivery system.

- ? Guidance on methods for determining whether a REMS with ETASU is commensurate with the risks and not unduly burdensome on patient access.

Value of Standardizing REMS Assessments



- Less uncertainty for Sponsors about what to measure and how
- Cross program comparisons
- Shared understanding of more or less effective program elements
- Basis for assessing if ETASU is commensurate with risk and is or is not unduly burdensome
- Basis for assessing basis for REMS modification or elimination

Conclusion

- A science-based, healthcare intervention assessment framework for assessing REMS can be envisioned
  - Addresses factors and follows principles
  - Potentially generates more comprehensive, actionable information
  - Informs the development of industry guidance
- FDA will validate proposed framework against prior programs
- Stakeholder feedback continues
- Guidance development is being initiated

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REMS Assessments: A Summary of FDA's Experiences and Challenges

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Goals of Today's Presentation

- Review REMS assessment practices
- Provide insights into what we have heard and learned about REMS assessments

Outline

- Overview of REMS assessment
  - Goals
  - Assessment process, methods, and metrics
  - Social science workshop
- Example: REMS assessments of teratogenic drugs
- Conclusions

REMS Goals

- FDAAA requires that the REMS assessment includes a determination about whether the program is "meeting its goals"
- Goals for the REMS are variable
  - Almost all REMS include a goal to inform prescribers and usually patients about the relevant risks
  - REMS with Elements to Assure Safe Use (ETASU) may have additional goals
    - To minimize certain risks (e.g., teratogenicity, myocardial infarction)
    - To limit use to certified prescribers or certain patients
    - Ensure compliance with certain testing or other conditions of safe use.

Methods/Metrics Used in REMS Assessments

- Communication Plan (CP) and/or Medication Guide (MG) use data from:
  - Knowledge, Attitude and Behavior (KAB) surveys
    - Knowledge and understanding of serious risks and safe use conditions (prescribers and patients)
    - Knowledge of proper patient selection (prescribers)

Methods/Metrics Used in REMS Assessments - 2

- REMS with ETASU may collect data on:
  - Processes
    - Compliance with REMS requirements - implementation
      - Number of enrolled/certified prescribers, patients, pharmacies
      - Number of prescriptions by non-enrolled prescribers
      - Number of Dear Healthcare Provider letters mailed
      - Corrective actions taken to address non-compliance
    - Compliance with REMS requirements - safe use conditions
      - Number of times patients had not completed required laboratory testing
      - Number of pre-infusion patient checklists received that suggest patient should not be treated
  - Root Cause Analysis (RCA) (e.g., reasons for pregnancy)

Methods/Metrics Used in REMS Assessments - 3

- REMS with ETASU may collect data on:
  - Utilization
    - Demographics of patients and prescribers (e.g., specialty)
    - Use in population at risk (e.g., female of reproductive potential)
    - Prescribing behaviors (e.g., prescribing high dose opioids to non-tolerant patients)
  - Outcomes
    - Number/rate of adverse events that REMS is attempting to either mitigate (e.g., number of pregnancies) or detect (e.g., PML)

Challenges with Assessing REMS

- Many of the goals and metrics focus on process and not outcomes of the REMS
  - Many outcomes are difficult to measure because there are no pre-REMS data or other good comparator data, outcomes are often rare events, and drug use may be limited
  - Measures of behaviors that might be indicators of success, such as use of a contraceptive while taking a teratogen, or determining whether patients were counseled, can also be difficult to obtain
  - It is difficult to associate particular REMS interventions with specific actions.

Challenges with Assessing REMS

- Assessment of access and burden imposed by REMS has not been a required component of a REMS assessment
- Information from REMS assessments that might help evaluate access and burden
  - Call center data
  - Shipment delays from specialty pharmacies
- The Agency continues to explore valid metrics for quantifying access and burden considerations
  - Stakeholder input sought

Surveys and Survey Methodology: Social Science Workshop - Stakeholder Feedback*

- Discussed the validity and salience of patient, prescriber and pharmacist surveys as required components of REMS assessments
- Discussed methods to assess REMS goals related to knowledge
- Discussed potential alternatives to assess knowledge

*June 7, 2012: http://www.fda.gov/Drugs/NewsEvents/ucm292337.htm

Social Science Workshop Panels

- Panel 1:
  - Survey endpoints
  - Recruitment and sample size
  - Question design
  - Process Issues
- Panel 2:
  - Alternatives to surveys to assess patient and health care provider knowledge
  - Input on how surveys and other tools could be used to assess healthcare system burden and patient access imposed by REMS

Social Science Workshop: Panel 1

- Panel 1 feedback (workshop and docket comments)*
  - Clearly identify key risks
  - Knowledge rate of 80% appropriate in most instances
  - Centralized website for recruitment suggested
  - Keep surveys short (10 minutes)
  - Develop standardized questions for evaluating REMS outcomes
  - Pretesting of surveys is essential
  - Educational materials should be tested for comprehension
  - Surveys have challenges and limitations, but are the best option for testing knowledge

*Not comprehensive

Social Science Workshop: Panel 2

- Panel 2 feedback (workshop and docket comments)*
  - Use complimentary data sources to surveys
  - Consider systems engineering approach (FMEA) to address burden and costs
  - Explore the use of data mining and geographic mapping for access issues
  - Evaluation of behavior believed by some to be more important than knowledge
    - Test knowledge first, then measure behavior change

*Not comprehensive

Methods/Metrics Used in REMS Assessments: Example

- 2012 Drug Safety and Risk Management Advisory Committee Meeting*
  - Provided summary of aggregate analysis of REMS assessments for a group of teratogenic drugs
  - Discussion of
    - Decision framework that includes factors that should be considered when selecting risk management approaches for teratogenic drug products
    - Contraception and pregnancy testing recommendations to minimize risk of teratogens

*December 12 and 13, 2012: http://www.fda.gov/AdvisoryCommittees/Calendar/ucm325571.htm

Aggregate Analysis of REMS Assessments for Teratogenic Drugs

- 7 of 9 REMS programs with assessments submitted:
  - 1 MG and CP
  - 1 CP only
  - 5 ETASU (all have MG)
- Information for patients and prescribers on teratogenic risks and safe use conditions
- REMS with ETASU
  - Linkage of negative pregnancy test to dispensing

REMS Assessments for Teratogenic Drugs – Knowledge (n=7)

- Prescribers
  - >80% knowledge rate for teratogenic risks
  - Lower performance on specifics of recommended contraception
- Patients
  - >80% knowledge rate for teratogenic risks
  - Lower performance on specifics of recommended contraception

REMS Assessments for Teratogenic Drugs – Outcomes (n=5)

- 250,000 women treated
- 187,000 FRP treated→335 pregnancies reported
  - Estimated pregnancy rate across the REMS programs
    - 0-11 pregnancies/1000 FRP treated/year
  - Estimated unintended pregnancy rate, U.S. population*
    - 52 pregnancies/1000 women ages15-44/year (2006)
  - Comparisons of patients from REMS programs with U.S. population are problematic

*Finer LB, Zolna MR.
Contraception 2011;84:478-85

REMS Assessments for Teratogenic Drugs: Data Limitations

- Underreporting of pregnancies
  - Patients/prescribers may not be motivated
  - Patient/prescriber may feel reporting unnecessary if pregnancy terminated
  - Fear of reporting pregnancy
- Complete information about pregnancy often missing
  - Unable to reach patient or prescriber
  - Unable to determine if exposure occurred

REMS Assessments for Teratogenic Drugs: Root Cause Analysis (n=5)

- Methodology
  - Third party or prescriber
  - Telephone or office visit
  - Multiple outreach attempts to patient or prescriber
- Potential root causes of pregnancy
  - System problem
  - Poor understanding of recommended contraception
  - Non-compliance

REMS Assessments for Teratogenic Drugs: Root Cause Analysis – 2

- Root causes identified
  - Most common - failure to comply with recommended birth control
  - Other - Contraceptive failure
- Limitations
  - Incomplete information
  - Low participation
  - Timing of exposure unclear

Summary of Aggregate Analysis of REMS for Teratogenicity

- Data from REMS assessments suggest the REMS for the 5 drugs with ETASU are meeting the program goals
  - Low pregnancy rates
  - Good understanding of risks
- Further study needed to determine appropriate metrics to evaluate access and burden issues associated with REMS for teratogenic drugs

Conclusions

- FDA is working to develop better REMS goals and metrics to use when assessing REMS
- Increasing experience with REMS assessment has helped identify challenges that need to be addressed to more effectively assess these programs
- Also working to standardize the assessment plans as much as possible