Background Materials

REMS Standardization and Evaluation Public Meeting

Contents

1 Introduction

On July 25 and 26, 2013, FDA will hold a public meeting on the standardization and evaluation of Risk Evaluation and Mitigation Strategies (REMS). The purpose of this public meeting is to obtain feedback from stakeholders on: (1) issues and challenges associated with standardizing and assessing REMS for drug and biological products and (2) identifying potential projects that will help standardize REMS and integrate them into the health care delivery system. FDA is seeking information and comments from a broad range of stakeholders, including health care providers, prescribers, patients, pharmacists, distributors, drug manufacturers, vendors, researchers, standards development organizations, and the public.

To help prepare this meeting, FDA has developed this background document to familiarize stakeholders with our experience with REMS since they were first introduced in 2007.

1.1 REMS Regulatory History and Previous Stakeholder Feedback

1.1.1 REMS Regulatory History

REMS were introduced by the Food and Drug Administration Amendments Act (FDAAA) of 2007.[1] FDAAA authorizes FDA to require a REMS for a drug if the FDA determines that a REMS is "necessary to ensure the benefits of the drug outweigh the risks of the drug." The law authorizes FDA to require sponsors submitting new drug applications (NDAs), abbreviated new drug applications (ANDAs), or biologics license applications (BLAs) to submit a proposed REMS as part of such application, if the FDA determines that a REMS is necessary. FDAAA also authorizes FDA to require holders of applications approved without a REMS to submit a proposed REMS if the FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweighs its risks. Sponsors may also propose a REMS for their drugs at any time and submit this proposal to FDA.

Before FDAAA was enacted, FDA approved a small number of drug and biological products with risk minimization action plans (RiskMAPs). Like a REMS, a RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. Many of the principles used to develop RiskMAPs are embodied in the FDAAA REMS provisions as implemented by FDA. Certain products with RiskMAPs that contained elements to assure safe use that were in place prior to the enactment of FDAAA, were deemed to have, in effect, a REMS, and have been or will be converted to a REMS.

If appropriate, a REMS may be approved with elements to assure safe use, otherwise known by its acronym "ETASU." REMS with ETASU are discussed in various contexts throughout this document. ETASU are established to mitigate a specific and serious risk listed in the labeling of the drug. Depending on the risk, ETASU might include one or more of the following: health care providers who prescribe the drug have particular training or experience, or are specially certified; pharmacies, practitioners, or health care settings that dispense the drug are specially certified; the drug may be dispensed only to patients in certain health care settings (such as in hospitals or infusion centers); the drug is dispensed to patients with evidence or other documentation of safe-use conditions (for

[1] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm

example, liver enzyme tests, pregnancy tests); each patient using the drug may be subject to certain monitoring; or each patient using the drug must be enrolled in a registry.

1.1.2 Previous Stakeholder Feedback on REMS

FDA has regularly sought and received stakeholder feedback with regard to REMS in a variety of forums. In July 2010, FDA held a public meeting to obtain input on issues associated with the development and implementation of REMS. In June 2012, FDA held a public workshop to discuss survey methodologies and instruments that can be used to evaluate patients' and health care providers' knowledge about the risks of drugs marketed with an approved REMS.

Additionally, FDA has received feedback at a number of advisory committee meetings. FDAAA requires the Agency to bring, at least annually, one or more drugs with REMS with ETASU before the Drug Safety and Risk Management Advisory Committee (DSaRM) to discuss whether the REMS with ETASU assures safe use, is or is not unduly burdensome to patient access, and to the extent practicable, minimizes the burden to the healthcare delivery system. FDA also regularly discusses both pre- and post-approval REMS with ETASUs with various FDA advisory committees when discussing specific product applications.

In 2011, FDA created the REMS Integration Initiative (see Section 1.2), designed to review and improve the agency's implementation of REMS authorities. A key component of this initiative is stakeholder outreach; through the REMS Integration Initiative, FDA is engaged in ongoing outreach to a wide range of stakeholders to understand how existing REMS programs are working and where opportunities for improvement lie. For example:

- On March 8, 2013, FDA hosted a meeting with PDUFA stakeholders to inform them of the activities of the REMS Integration Steering Committee's three Workgroups and to hear their comments on REMS.[2]
- From April through June 2013 FDA held a series of fifteen teleconferences with patients and their caregivers, pharmacists working in diverse inpatient and outpatient care settings, prescribers, and about their experience with REMS.
- On May 16, 2013, the Drug Safety Oversight Board held a meeting with the Agency's federal partners, including the Veterans Health Administration, Department of Defense, National Institutes of Health, Agency for Healthcare Research and Quality, and the Indian Health Service. FDA's federal partners offered feedback about how well REMS programs were working for them, and where they saw opportunities for standardization and better integration into their systems.[3]
- On May 23, 2013 FDA participated in a conference on REMS sponsored by Trends Emerging in Risk Management (TERM). At this conference, FDA discussed its REMS assessment framework and received comments from risk management experts drawn from academia, industry and government.[4]

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[2] Minutes of the March 8, 2013 PDUFA stakeholder meeting are available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM350913.pdf

[3] Summary of the May 16, 2013 Drug Safety Oversight Board meeting available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm360049.htm

[4] The agenda for this summit is available at http://coral.ie.lehigh.edu/~TERM-SUMMIT/

FDA is also exploring options for expert panel discussion of standardized methods for assessing and characterizing risks and selecting appropriate REMS tools and interventions. In addition to the meetings and teleconferences noted above, FDA announced the opening of a docket, FDA-2013-N-0502, in the May 22, 2013 Federal Register notice of the July 25-26 public meeting on REMS, to receive public comments on REMS.[5] This docket will remain open indefinitely, so that stakeholders can continue to submit their comments after the July 25-26 public meeting. (Please note that although the docket will remain open indefinitely, FDA will not be able to consider comments submitted after September 16, 2013 in the report on REMS standardization that will be published in 2014.)

1.2 The REMS Integration Initiative

The goals of the REMS Integration Initiative are to develop guidance on how to apply statutory criteria to determine when a REMS is required, to improve standardization and assessment of REMS, and improve integration of REMS into the existing and evolving healthcare system.

To support the REMS Integration Initiative, the FDA Center for Drug Evaluation and Research (CDER) REMS Integration Steering Committee (RISC) oversees the activities of three workgroups focusing on issues related to REMS policy, REMS evaluation, and REMS design and standardization. Deliverables include fulfillment of commitments FDA made under the Prescription Drug User Fee Act (PDUFA V),[6] reauthorized on July 9, 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012.[7]

1.1.1 REMS Policy Workgroup

The REMS Policy Workgroup is developing a draft guidance to provide information about how FDA applies the factors specified in Section 505-1(a) of the Food, Drug and Cosmetic Act (FDCA), as well as other factors, to determine whether a REMS is necessary to ensure that the benefits of a drug outweigh the risks. FDA expects to publish this draft guidance in 2014. The guidance will incorporate the 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. The guidance will also provide information about when it may be appropriate to employ measures other than a REMS to address a serious risk. FDA is considering the important characteristics of a drug and its serious risk(s) that would suggest product labeling is insufficient to communicate the drug's risks and conditions of safe use, thereby failing to provide reasonable assurance that the risks will be appropriately managed within the existing healthcare setting. Information about the specific aspects of the healthcare delivery system that indicate certain REMS elements and/or tools are unnecessary or otherwise redundant is also of interest to FDA, as is the level 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.

1.1.2 REMS Evaluation Workgroup

The Evaluation Workgroup is developing an evidence-based approach, including a REMS Assessment Framework, to assess the effectiveness and burden of REMS. The Workgroup is soliciting stakeholder input on ways to set appropriate goals/objectives and performance levels for REMS, and appropriate metrics and measurement systems assessing performance and improvements for behaviors, outcomes,

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[5] www.gpo.gov/fdsys/pkg/FR-2013-05-22/pdf/2013-12124.pdf

[6] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm

[7] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/default.htm

burden and access. FDA expects to publish a draft guidance on evaluation methodologies in 2014. Additional details about the information needs of the Workgroup and the report are included in the Federal Register Notice.[8]

1.1.3 REMS Design and Standardization Workgroup

The REMS Design and Standardization Workgroup is working to reduce unnecessary variation in REMS by establishing best practices in the design and implementation of REMS. The workgroup recognizes that some variation in REMS is necessary and unavoidable: The risks that REMS seek to address vary, as do the patient populations and settings in which those drugs are used, leading to significant variation in how those risks should be addressed. However, there are cases in which common standards and "best practices" can be established and applied across a range of REMS to make REMS more predictable, more effective, and less burdensome to healthcare providers and patients.

With that in mind, the standardization workgroup has embraced two key goals as it seeks to standardize REMS: (1) the Workgroup seeks to develop standardized and evidence-based methods to characterize risks and identify appropriate interventions so that REMS that address similar risks in similar settings will use similar approaches to mitigate that risk, and (2), to identify and incorporate best practices to maximize the effectiveness of specific REMS tools and minimize their burden. A key part of achieving the second goal is ensuring that these specific REMS tools are integrated into the existing, evolving, and increasingly electronic health care delivery system.

[8] www.gpo.gov/fdsys/pkg/FR-2013-05-22/pdf/2013-12124.pdf

2 General REMS Background

2.1 Development of REMS

Once FDA determines that a REMS is necessary to ensure the benefits outweigh the risk, FDA communicates the requirement for the REMS, including the necessary REMS elements (e.g., communication plan REMS, ETASU), to the applicant. The applicant submits a proposed REMS that includes the goals of the REMS, the required elements, and the specific REMS tools (e.g., letters to healthcare providers and professional societies, healthcare provider and patient certification, documentation of safe use conditions). The applicant also includes a proposal for how it plans to assess the effectiveness of the REMS (assessment plan).

FDA reviews the REMS proposal and discusses details of the REMS with the sponsor, including implementation and assessment plans. REMS programs are developed by the individual sponsors and the specifics of these programs are negotiated between the sponsors and FDA. As the REMS is being developed sponsors may engage stakeholders in the development of REMS. For products that are not yet approved, FDA is limited in its ability to discuss a proposed REMS with stakeholders because of the confidential nature of the drug review process.

2.2 Approval of REMS

When a REMS is approved, FDA sends a letter to the sponsor documenting approval of the REMS. These letters describe and clarify the risks that the REMS is intended to mitigate and include a description of the REMS and REMS Assessment Plan. When a REMS is approved, it is the responsibility of the sponsor to implement the REMS program.

Every REMS includes a timetable for submission of assessments of the REMS. Sponsors are required to submit the assessment of their REMS according to the dates specified in the timetable. The statute does not specify how the REMS should be assessed, only that that an assessment of a REMS for a drug shall include, with respect to each goal included in the REMS, an assessment of the extent to which the REMS, including each REMS element, is meeting the goal or whether one or more such goals or elements should be modified.

FDA reviews REMS assessment reports to evaluate whether the REMS is meeting its goals. There are challenges when evaluating the effectiveness of REMS because outcome data are often incomplete or unavailable. Since many drugs with a REMS were approved with a REMS in place, a "pre-REMS" comparison cannot be made. Even when REMs are implemented postmarketing, there are often insufficient data and problems comparing the pre- and post-REMS periods. FDA's experience with REMS assessments is described in greater detail in section 4.2, "Current Methods for Assessing REMS."

A REMS may need to be modified in response to a REMS assessment, a reassessment of a product's benefit-risk profile at the time of approval for a new indication, or the emergence of new safety information. REMS modification may comprise addition, removal, or otherwise changing of any goal, element, or tool of the approved strategy.

2.3 The Content of a REMS Submission

The REMS that are submitted and approved by FDA take the form of a series of documents and materials, which FDA makes available to the public at its approved REMS website. The REMS includes

the goals of the REMS, the REMS elements and the requirements under those elements, and the REMS tools.

The Goals section of the REMS document describes the desired safety-related health outcome of the REMS. The format of goals has varied significantly, but goals are often divided into two sections: a heading that describes the overall desired safety or health outcome, and sub-headings that describe the means by which this goal is achieved.

The Elements section of the REMS document describes all of the major components of the REMS, which may include a medication guide, communication plan, ETASU, or an implementation system. REMS for NDAs and BLAs must include a timetable for submission of assessments.

Within the ETASU section of the REMS document are a number of sub-headings describing specific aspects of the REMS' ETASU. These sub-headings often provide a good overview of the high-level requirements that stakeholders must meet. The language used in the sub-headings is often similar to the language used in section 505-1(f)(3)(A-F) of the Food, Drug and Cosmetic Act to describe FDA's authorities to require ETASU, but the content of the sub-headings do not necessarily correspond directly to those authorities.

In addition to the REMS document, FDA also reviews and approves "Appended Materials," which are materials directed towards healthcare providers and patients. These include administrative forms such as enrollment forms for prescribers, patients, and dispensers, as well as training and educational materials. Specific types of appended materials are described in REMS Tools, (see section 3 of this document.)

Details about REMS implementation are typically included in the REMS Supporting Document. The REMS Supporting Document also includes the sponsor's proposed REMS assessment plan. The REMS Supporting Document is not made available on FDA's REMS website.

Once approved, the REMS document and the appended materials are the basis for enforcement of the REMS.

3 REMS Tools

A REMS "tool" is a process or system designed to ensure that certain safe use conditions are in place so that prescribers, pharmacists (or other dispensers) and/or patients are aware of the serious risks of the drug and carry out any specific requirements needed to mitigate those risks. The Federal Register notice that announced this public meeting included a number of questions about REMS tools. To help stakeholders answer these questions, this section includes a description of each REMS tool's important features, and provides examples of how each tool has been used.

Disclaimer: This section of the document represents FDA's initial efforts to systematically characterize variation across REMS. This section seeks to describe REMS tools and their use in REMS programs as accurately as possible, but given the scope, scale, and diversity of REMS programs and tools, it cannot guarantee that the information contained in this document is complete and reflects the most current REMS documents and materials. Healthcare providers and patients who need information about a particular REMS program should refer to the information and materials provided by the drug manufacturer. Up-to-date information on REMS programs is also available on FDA's approved REMS website.

The tools described in this section of the document are organized into the following categories:

Tool Category	Description / Purpose	Example Tools
3.1 Communications to Healthcare Providers	Tools used to disseminate information to healthcare providers to help ensure they are aware of the REMS and their responsibilities within the REMS	Dear Healthcare Provider Letters, Websites, Journal Information Pieces
3.2 Training of Healthcare Providers	Tools that ensure that healthcare providers understand the drug's risks, how to use the drug safely, and what the REMS requirements are.	Training Materials, Overviews, Prescribing Information
3.3 Enrollment and Certification of Healthcare Providers	Tools that ensure that healthcare providers meet all necessary requirements to be able to safely prescribe, dispense, and/or administer the drug.	Prescriber and Dispenser Enrollment Forms
3.4 Initiation of Therapy and Patient Counseling	Tools that ensure that patients and prescribers make informed benefit-risk decisions, that patients understand how to use the drug safely, and that appropriate screening and patient selection takes place.	Patient-Prescriber Agreements, Patient Educational Materials, Medication Guides, Counseling Tools
3.5 Ongoing Patient Care	Tools that ensure that healthcare providers and patients meet safe use conditions, are appropriately monitored, and carry out REMS requirements.	Patient Monitoring, Verification of Safe Use Conditions

3.6 Adverse Event Reporting	Tools that facilitate the reporting and collection of information on adverse events of interest.	Patient Registries, Adverse Event Reporting Forms
3.7 Distribution Controls	Tools that ensure that only certified and/or enrolled parties can obtain the drug.	Distributor enrollment Forms

3.1 Communications to Healthcare Providers

REMS communications are messages that are delivered to healthcare providers in the form of letters, articles, and other media. Communications are designed to make healthcare providers aware of the serious safety issue, the REMS requirements, and where they can go to get more detailed information. Communications are not designed to provide comprehensive information about safe use of the drug or directly support the completion of REMS requirements.

REMS communications are included in the approved REMS. In many cases, communications are issued as part of a REMS' communication plan, which is directed towards prescribers and other healthcare providers and specifies the audience that should receive the communication, the key messages to be delivered, the frequency of the communication and the medium through which the communication will take place. Communications may also be included as part of a REMS' ETASU.

To date, REMS have used just a few different communication tools, including letters, websites, and journal information pieces.

3.1.1 Letters

The most frequently-used form of REMS communication is the letter. Letters may be delivered directly to healthcare providers or to the healthcare providers though professional societies that represent them.

Letters to healthcare providers, often referred to as Dear Healthcare Provider Letters (DHCPs) may cover any topic related to the REMS, but are most frequently sent when a REMS is first approved to make healthcare providers aware of the existence of the REMS and the safety issue that the REMS is intended to mitigate. Other letters may be used to inform or remind healthcare providers of specific REMS requirements, new safety information, changes to the REMS, or the availability of certain REMS materials.

In addition to sending letters to individual healthcare providers, a few REMS programs send letters to professional societies that represent healthcare providers who are likely to use the drug. Like letters to individual healthcare providers, these letters are typically sent when a REMS is first approved to make the societies aware of the existence of the REMS and the safety issue that the REMS is intended to mitigate, and encourage professional societies to share this information with their members.

Key Features of Letters:

- **Delivery method**: Letters may be delivered to healthcare providers by mail, e-mail or both. Many sponsors use their field representatives to deliver these letters along with other REMS communications and REMS materials, but the use of field representatives is not usually required as part of the REMS.
- **Frequency of letters**: Most letters are sent when a REMS is first approved, however there have been some REMS that have required annual delivery of the letter for a period of time such as the first three years of approval of the REMS. There are also REMS letters that are sent to any new healthcare provider that decides to enroll in the REMS program.

Examples:

- Extended Release / Long-Acting (ER/LA) Opioids: First Prescriber Letter
- Transmucosal Immediate-Release Fentanyl (TIRF): Dear Outpatient Pharmacy Letter
- Adasuve: Dear Healthcare Professional Letter
- Caprelsa: Dear Medical Society Letter

3.1.2 Websites

REMS usually include websites that provide general information about the REMS program, and may include online versions of REMS materials such as enrollment forms and training materials as well as downloadable print forms and materials. Websites that are part of a REMS are kept distinct from websites the sponsor may use for promotional purposes.

Examples:

- Mycophenolate: REMS Homepage Screenshots
- Pomalyst, Revlimid, Thalomid: CelgeneRiskManagement.com Screenshots
- Juxtapid: REMS Website Screenshots

3.1.3 Journal Information Pieces

Several REMS include journal information pieces to raise awareness of a drug's risks and/or its REMS. These pieces are typically published in leading journals that target the medical specialties most likely to prescribe the drug or to treat patients who are taking the drug (e.g., prescribers who are likely to treat patients experiencing an adverse event associated with the drug). These pieces may also be shared at scientific meetings that prescribers are likely to attend.

Examples:

- Mycophenolate: Journal Information Piece
- Stelara: Journal Information Pieces
- Actemra: Journal Information Pieces

3.2 Training of Healthcare Providers

Currently, all REMS with ETASU include training or education for healthcare providers (e.g., prescribers and/or dispensers). REMS training provides information about the risks associated with the drug, how to use the drug safely, or the requirements of the REMS program. Training is almost always required for REMS that require healthcare provider certification (see below for more details about HCP certification)[9]

The sponsor is usually responsible for making training available to individual healthcare providers, and often append the training materials to REMS communications. But when REMS provide training to healthcare settings, the designated healthcare setting representative typically takes responsibility for training that healthcare facility's staff.

Most REMS training is directed towards the healthcare providers who prescribe, dispense, and administer the drug. But the training may also be required for staff within a healthcare setting who are

[9] …with the exception of the REMS for Isotretinoin, Mifeprex, Pomalyst, Revlimid, Thalomid, Tikosyn, Versacloz. (Note that in the Tikosyn REMS, prescribers are asked to review certain training materials before prescribing, even though this requirement is not in the REMS document).

involved in the care of the patient who is taking the drug, including those who counsel, monitor, or treat patients.

A variety of tools have been used to train healthcare providers, including REMS program overviews and training materials such as slide decks and program brochures. Training tools provide information about the risks associated with the drug, how to use the drug safely, and/or the requirements of the REMS program. In some cases, all of this information is captured in a single tool; in other cases, the training tools may be augmented with other tools that the healthcare provider can use to reinforce particular parts of the training or to reference at later time.

The REMS for extended-release/long-acting opioid analgesics makes training available to prescribers through continuing education (CE) providers. The CE providers develop the training based on an FDA Blueprint for Prescriber Education. Using CE to deliver educational programs required under REMS may create additional incentives for the healthcare community to educate themselves and allow FDA and sponsors to leverage accredited CE providers' expertise to develop effective educational tools. The CE component of the REMS for the extended release/long-acting opioid analgesics is FDA's first experience using CE as the tool for prescriber education required as part of a REMS. The lessons FDA learns with implementation will help inform future planning for REMS and CE.

Examples:

- ER/LA Opioids: FDA Blueprint for Prescriber Education

3.2.1 Training Materials

REMS training programs and/or materials are educational tools that are designed to provide healthcare providers with comprehensive training on the risks addressed by the REMS, how to mitigate those risks, and what the healthcare provider's requirements are under the REMS. REMS programs may have one or multiple training materials. Healthcare providers are usually expected to review training materials prior to prescribing or dispensing a drug, and may be supplemented by other tools to be used in the course of clinical care.

As mentioned previously, the review of training materials is an important requirement for healthcare provider certification in many REMS. However, some REMS include healthcare provider training but do not require healthcare provider certification. In some of these REMS, the healthcare provider may be asked to fill out a training confirmation form to track which prescribers have completed the training. Prescribers of Mycophenolate and Qysmia, for example, are asked to complete forms to confirm that they have received training.

REMS training materials are based on, but distinct from, the FDA-approved prescribing information. Like prescribing information, training materials provide detailed information about the drug's risks and how to use the drug safely; but unlike the prescribing information, the training materials tend to focus on the specific, serious risk targeted by the REMS. Training materials also provide detailed information about the operation of the REMS program that may not be found in the prescribing information.

Key Features of Training Materials:

- **Format**: Training materials may be formatted as written guides, brochures, slide decks, or transcripts for delivery by a trainer.
- **Delivery**: The materials may be delivered to healthcare providers in a variety of ways: print materials may be mailed or handed to a healthcare provider, training may be made available

online, or training may be provided by a trainer in person or over the phone. Healthcare facilities that train their own staff are typically free to use a range of methods to deliver the training.

- **Knowledge Assessments**: Some training materials incorporate knowledge assessment questions into the training.

Examples:

- Juxtapid: Prescriber Training Module
- Isotretinoin: Pharmacist Guide

3.2.2 Prescribing Information

FDA-approved prescribing information (also known as "PI" or "labeling") contains comprehensive information on a drug's indications, usage, and risks, including risks that are not targeted by the REMS. The prescribing information may also include a medication guide. Healthcare providers are always encouraged to read the prescribing information in addition to participating in any other REMS training, and some REMS require prescribers to acknowledge that they read the prescribing information in order to become certified. Even though prescribing information may play an important role in the REMS, it is not usually part of a REMS' appended materials and is not reviewed as part of the REMS.

Examples:

- Letairis: Prescribing Information (not part of the REMS)
- Sabril: Prescribing Information (not part of the REMS)

3.2.1 Program Overviews

Program overviews are documents that help healthcare providers understand how the REMS program operates and what their responsibilities are within the program. They are generally found only in REMS that require healthcare providers to be certified. They are often designed to serve as a succinct reference tool, rather than as a source of comprehensive information.

Examples:

- Entereg: Program Overview

3.2.2 Knowledge Assessments

A few REMS include post-training knowledge assessments, typically in the form of multiple-choice questions. These knowledge assessments should not be confused with the Knowledge, Attitude and Behavior (KAB) surveys that sponsors use to conduct their REMS assessments. Post-training knowledge assessments can help assess healthcare providers' understanding of REMS training materials, reinforce key training messages, and ensure that the prescriber understands the drug's risks and how to use the drug safely. Completion of knowledge assessments may be required in order for a healthcare provider to become certified. When knowledge assessments are included in training materials, they may take place at the end of the training, or assessment questions may be interspersed throughout the training.

Key Features of Knowledge Assessments:

- **Criteria for successful completion**: REMS usually require prescribers to get a certain number of questions right in order to successfully complete the knowledge assessment. If a prescriber

answers a question incorrectly, prescribers may be offered another opportunity to answer the question or may be presented with a different question. One REMS temporarily blocks prescribers from being able to enroll in the REMS if they are unable to successfully complete the knowledge assessment after 3 attempts.

- **Feedback on answers**: In some cases, healthcare providers receive feedback on incorrect answers explaining why their answer was wrong and presenting additional training material relevant to that question. When healthcare providers take knowledge assessments on-line, in person, or over the phone they may receive instantaneous feedback on their answers, but feedback can take significantly longer when knowledge assessments are submitted via fax or mail.
- **Knowledge assessments developed by CE providers**: The REMS for extended-release/long-acting opioids includes knowledge assessments that are developed and administered by the continuing education providers who provide the REMS training

Examples:

- Qsymia: Print Training and Knowledge Assessment
- TIRF: Knowledge Assessment

3.2.3 Other Training Tools

In addition to prescribing information, REMS overviews, and training materials, REMS may include additional training tools designed to address specific issues related to safe use of the drug.

One important type of training tool is the "enabling tool." Certain tools such as checklists and counseling guidelines help prescribers apply their learning to practice, and support ongoing care of patients.

Examples:

- Mycophenolate: Prescriber Training Confirmation Form
- Soliris: Dosing and Administration Guide
- Truvada: Checklist for Prescribers
- Tysabri: Understanding PML for Gastroenterologists

3.3 Enrollment and Certification of Healthcare Providers

In most REMS with ETASU, healthcare providers must complete certain REMS requirements in order to be able to prescribe, dispense, or order a drug. Once a healthcare provider or setting has met these requirements, they are referred to as "certified." For healthcare providers who prescribe the drug, the process for obtaining this certification is referred to as "prescriber certification," and for healthcare providers and settings that dispense the drug, this process is referred to as "dispenser certification."

In order to become certified, healthcare providers must meet a number of requirements. Nearly all approved REMS require that healthcare providers enroll in the REMS by providing basic demographic information to the REMS program (typically through the use of an enrollment form). Those that do require healthcare providers to enroll also require them to acknowledge that they understand the drug's risks and how to use the drug safely and agree to follow certain REMS requirements when treating patients with the drug. In addition, REMS with prescriber certification may require that providers acknowledge or demonstrate (for example, via a knowledge assessment) that they possess certain experience or abilities (e.g., the ability to diagnose or treat certain adverse events), have completed REMS-required training, or that they have systems in place to ensure and document the

completion of REMS requirements. Prescriber certification is often verified by pharmacists prior to dispensing medication to verify safe use as part of a REMS.

REMS may require the certification of an individual provider, as described above, or of an entire healthcare setting or organization. At this time, all REMS that require prescriber certification certify individual prescribers, while all REMS that require dispenser certification certify the entire dispensing setting. In order for a setting to become certified, it must designate a health care setting representative to manage that setting's certification and enrollment in the REMS.

Key Features of Healthcare Provider Enrollment and Certification:

- **Setting-specific certification**: In REMS that include certification of dispensing settings, the requirements that a setting must meet depends on the role that the setting plays in the distribution, dispensing, and administration of the product. For example, the REMS for Zyprexa Relprevv and Tysabri have multiple types of dispenser certification, including separate certifications for dispensers who dispense the drug but do not administer it and for settings in which the drug is administered directly to patients. In addition, certain settings may be exempted from REMS requirements. For example, the risks that the TIRF REMS seeks to address, such as accidental exposure and overdose, are more easily managed in the inpatient setting. As a result, prescribers do not need to become certified in order to prescribe TIRF products to inpatients, and some of the requirements that the REMS places on dispensers applies only to those who dispense TIRFs to outpatients.
- **Indication-specific certification**: The safety profile of a product may vary by indication and patient population. Therefore, certain REMS certification requirements may vary. For example, even though ESAs have multiple indications, the risk addressed by the ESA REMS is specific to its use in cancer patients, and the REMS only requires certification of healthcare providers and settings that wish to prescribe or dispense ESAs to cancer patients. Similarly, certain aspects of certification for the Tysabri REMS differ depending on whether the prescriber is treating patients with Multiple Sclerosis or Crohn's Disease.
- **Re-certification**: REMS may require healthcare providers and settings to be re-certified or to repeat certain certification requirements, such as training or the completion of an enrollment form. Most commonly, healthcare providers and settings must re-certify at regular intervals. In REMS with periodic re-certification requirements, the sponsor is usually asked to remind healthcare providers of the need to re-certify so that they do not experience any interruption in their ability to prescribe or dispense the drug.

Examples:

- List of REMS that require prescriber certification and the requirements that prescribers must meet in order to become certified (as of June 1, 2013)
- List of REMS that require dispenser certification and the requirements that dispensers must meet in order to become certified (as of June 1, 2013)

3.3.1 Enrollment Forms and Prescriber Agreements

Enrollment forms are used by healthcare providers to provide basic identifying and demographic information to the REMS programs. Enrollment allows sponsors to track which healthcare providers have been certified and communicate with them. Successful enrollment in a REMS may serve as evidence that a healthcare provider has met all requirements for certification and is therefore able to

prescribe or dispense the drug. For this reason, the terms "enrolled" and "certified" are often used interchangeably within REMS programs.

When filling out the enrollment form, healthcare providers are usually required to review and sign certain agreements and acknowledgments, which are included on the form. The specific content of these agreements and acknowledgments depends largely on the requirements of the specific REMS, and tend to fall into three major categories:

1) Acknowledgments that the healthcare provider has met certain requirements for certification.
2) Agreements that the healthcare provider will follow certain REMS requirements in the future.

In the forms, healthcare providers may also consent to receiving communications related to the REMS and to permit the sponsor to monitor or audit their compliance with the REMS.

All enrollment forms collect basic information about the healthcare provider and/or healthcare setting representative and their practice setting so that they can be tracked and receive communications from the REMS program. Most REMS also ask healthcare providers to submit a number that uniquely identifies them, such as a National Provider Identifier (NPI) number or, for prescribers, a State License Number. (Note: Some REMS may identify healthcare providers using DEA numbers for controlled substances).

Key Features of Enrollment Forms and Prescriber Agreements:

- **Link to certification**: All REMS that require certification also require that prescribers complete an enrollment form, but certain REMS may not provide dispensers with an enrollment form. Instead, dispensers that wish to become certified to dispense these drugs must enter into a contractual agreement with the manufacturer of the drug.
- **Combined prescriber-patient enrollment:** In most REMS, prescribers are asked to complete a dedicated prescriber enrollment form before they begin treating patients. The REMS for Tracleer and Tysabri, however use a single form to enroll both prescribers and patients in the REMS at the initiation of therapy. Both forms contain sections for both prescriber and patient enrollment. In the Tracleer REMS, prescribers must fill out the prescriber enrollment section of the form the first time they prescribe Tracleer to a patient. In the Tysabri REMS, the prescribers must fill out the enrollment section of the form every time they initiate treatment with a new patient.
- **Submission method**: REMS usually ask prescribers to print, sign, and submit enrollment forms through mail or fax. A small number of REMS permit prescribers to submit their enrollment forms online and do not require a handwritten signature.

Examples:

- Letairis: Prescriber Enrollment and Agreement Form
- ESAs (Aranesp, Epogen, Procrit): Enrollment Form for Healthcare Providers
- Zyprexa Relprevv: Buy & Bill Pharmacy Service Provider Registration Form
- Entereg: VA Medical Center Registration Form
- TIRF: Chain Pharmacy Enrollment Form

3.4 Initiation of Therapy and Patient Counseling

At the initiation of therapy healthcare providers may:

1. Counsel patients on the benefits and risks of different therapies and help them determine whether a REMS drug is appropriate
2. Counsel and educate patients on safe use of the drug
3. Solicit information about a patient's risk factors for an adverse event or, their likelihood of benefiting from the drug, to inform prescribing decisions

REMS may include educational materials and counseling tools to support each or all of these steps. After the decision to use a drug has been made, these same tools can help ensure that patients know how to use the drug safely. Tools such as patient-prescriber agreements and prescription order forms facilitate the screening of patients to ensure that they are appropriate candidates for therapy, and to document that safe use conditions have been met.

Examples:

- Erythropoiesis Stimulating Agents (ESAs) including Epogen, Procrit, and Aranesp may increase the risk of shortened overall survival or tumor recurrence in cancer patients. The REMS includes counseling tools and a patient-prescriber agreement for cancer patients to ensure that patients are aware of these risks when deciding whether to use ESAs.
- Before starting patients on Versacloz, a clozapine product, healthcare providers must document that the patient is appropriate (e.g., has not experienced serious adverse events with clozapine in the past) and are undergoing regular monitoring of white blood cell counts and absolute neutrophil counts. This documentation is accomplished using Versacloz' prescription order form at the initiation of therapy.
- For drugs that cause birth defects, prescribers may need to determine whether a female patient is able to get pregnant, in which case pregnancy monitoring may be needed. If that patient is already pregnant, it may not be appropriate to initiate treatment with that drug. For example, prescribers of Pomalyst, Revlimid, and Thalomid must classify the patient in one of six risk categories based on their potential to be sexually active and/or become pregnant. The REMS provides a different patient prescriber agreement and enrollment form for each risk category, and prescribers document the patient's risk category by submitting the appropriate form.

3.4.1 Counseling Tools for Healthcare Providers

REMS may provide healthcare providers with tools to help them counsel patients. This may include materials that are directed towards the prescriber, and it may also include material that can be shared with the patient and given to the patient after the counseling session. Counseling tools are most often used at the initiation of therapy, but may also be used to facilitate follow-up counseling.

For prescribers who want to refer patients for counseling, some REMS provide tools to facilitate this process. For example, the Mycophenolate REMS offers prescribers letters that can be used to refer patients for to an obstetrician/gynecologist for contraceptive counseling, and the isotretinoin REMS provides a version of its counseling guide for use in referrals.

Examples:

- Qsymia: Healthcare Provider Counseling Tool for Females of Reproductive Potential
- Gattex: Patient and Caregiver Counseling Guide
- Mycophenolate: OB-GYN Contraception Counseling Referral Letter

3.4.2 *Patient-Prescriber Agreements and Patient Enrollment Forms*

Patient counseling is frequently provided at the initiation of therapy to educate patients about the REMS, and patient-prescriber agreements are used to assist in this process and document that the counseling took place. When such agreements are used, the prescriber is usually responsible for ensuring that this form is completed and signed.

Like healthcare provider enrollment forms, these documents contain agreements and acknowledgments for patients and prescribers, and the content of the agreements may vary depending on the requirements of the specific REMS. These agreements may also serve as a patient enrollment form, providing patient information to the REMS program that allows the sponsor to track patients and ensure that only those who have completed the patient-prescriber agreement can obtain the drug.

A small number of REMS use "patient agreements" in lieu of patient-prescriber agreements. While similar in structure and purpose to the patient-prescriber agreement, they do not include prescriber agreements and do not require the prescriber to sign the form. The prescriber may still be responsible for ensuring that the patient reviews and signs this form.

Key Features of Prescriber-Patient Agreements and Patient Enrollment Forms:

- **Documentation of agreement**: Prescribers and/or healthcare settings may be asked to maintain a signed copy of the agreement in the patient's medical record. When the patient-prescriber agreement also acts as an enrollment form, prescribers may be asked to submit the completed document to the sponsor instead of or in addition to keeping it in the medical record.
  When prescribers are asked to place the completed agreement into the patient medical record, it can pose challenges for prescribers who use electronic health records, particularly in health systems that require forms to adopt a standardized format. Some programs allow prescribers to place an electronic scanned copy of the agreement into the record. The REMS for Epogen/Procrit and Aranesp allow healthcare settings to modify the enrollment form as needed to permit integration into electronic health records.
- **Prescription Order Forms**: Some patient-prescriber agreements also act as prescription order forms that allow prescribers to order a new prescription.
- **Medical history and screening**: Patient-prescriber agreements may also include questions about the patient's medical history to assist in the screening of appropriate patients and track how the drug is being used. This is discussed in greater detail in the "Documenting Safe Use Conditions" section of this document.

Examples:

- Sabril: Patient/Parent/Guardian-Physician Agreement Form
- Thalomid: Patient-Physician Agreement Forms
- ESAs (Aranesp, Epogen, Procrit): Guidelines for Patient Acknowledgment Form Integration
- List of REMS that include an enrollment or agreement form at the initiation of therapy (as of June 1, 2013)

3.4.3 *Medication Guides and other Patient Educational Materials*

Medication Guides are the most frequently-used patient educational materials in REMS. Medication guides generally are considered part of the REMS but are reviewed separately as part of the drug's prescribing information. Unlike other patient educational materials, the medication guide includes information on the drug's major risks – not just the risks that are being addressed by the REMS.

The use of medication guides predates REMS, and medication guides are used outside of REMS. Medication guides must be dispensed with the drug and in addition, when part of a REMS, with ETASU, prescribers will be instructed to use the medication guide as a counseling tool, to give the medication guide to patients when the drug is first prescribed, and, in some cases, to continue providing the medication guide on subsequent office visits.

Several REMS with ETASU use other patient educational materials to supplement the medication guide by discussing specific risks in greater detail.

Although it is not considered an educational material, the patient agreements found in certain REMS highlight key information that the patients need to know, and may help to reinforce other REMS educational material.

Key Features of Patient Educational Materials:

- **Format**: Among REMS with ETASU, nearly all patient educational materials are printed, written materials. One exception is the educational DVDs that are included in the iPLEDGE program.
- **Delivery method**: All medication guides are provided to patients by the dispenser of the drug, and, in REMS with ETASU, medication guides are often provided by the prescriber as well. Most other REMS educational materials are provided to the patient by the prescriber.
- **Length**: Patient educational materials vary in length. Currently, REMS medication guides may range from 1 to 8 pages. The ER/LA Opioid REMS counseling document is only one page, while other patient booklets and brochures may be 10 pages or longer.
- **Contraception Information**: All REMS for drugs that carry the risk of birth defects include guidelines on how to avoid becoming pregnant and include an overview of contraceptive options, but the format and content of the guidelines varies across REMS. (variations in FDA's approach to management of teratogenic risk addressed at an advisory committee meeting in December 2012)
- **Comprehension Questions**: REMS may include questions to confirm a patient's comprehension of key REMS messages.

Examples:

- Tysabri: Medication Guide
- ER/LA Opioids: Patient Counseling Document
- Thalomid: Patient Guide
- Isotretinoin: Patient Counseling DVD (script)

3.4.4 Prescription Order Forms

Certain REMS include prescription order forms. These forms are used to order product from a pharmacy and, while doing so, may remind prescribers of counseling, screening, and dosing requirements. Prescription order forms may be included as part of patient-prescriber agreements, allowing the dispensing pharmacy to easily verify that the agreement was completed when they receive the prescription.

Key Features of Prescription Order Forms:

- **Frequency of use**: Some prescription order forms are used only at the initiation of therapy, while others are used each time a patient needs a new prescription.

- **Custom forms for the Department of Veterans Affairs (VA)**: REMS include special prescription order forms to accommodate the requirements of the Department of Veterans Affairs. Patients who obtain treatment in the Department of Veterans Affairs need to submit their prescription to a specialty VA pharmacy and include VA-specific information on the prescription. Other government and integrated healthcare systems may need similar accommodations.
- **Documentation of safe use conditions**: Prescription order forms may allow prescribers to document and verify that safe use conditions are in place at the time of prescribing.

Examples:

- Kynamro: Prescription Authorization Form
- Pomalyst: Patient Prescription Form
- Rosiglitazone: VA Patient Enrollment Form

3.5 Ongoing Patient Care

Once the patient has been initiated on therapy, REMS may require ongoing monitoring to watch for adverse events and ensure that the patient remains an appropriate candidate for treatment. During this phase, healthcare providers may be required to:

1. Continue counseling patients and remind patients of safety messages
2. Continue to monitor for contraindications and adverse events
3. Periodically re-assess the benefits and risks of the treatment to ensure that the therapy remains appropriate

During this phase, additional counseling may be provided by the healthcare provider to reinforce any prior patient education and counseling. In addition, patients may receive additional copies of educational materials from the pharmacist or at subsequent office visits from the prescriber. Many REMS require routine monitoring to ensure that safe use conditions are in place, and REMS may include special tools and forms to ensure that this is happening, including documentation of safe use conditions by prescribers and dispensers, and verification of safe use conditions prior to dispensing.

- **Patient Comprehension Questions:** The REMS for Revlimid, Thalomid, Pomalyst, and Isotretinoin, include monthly patient comprehension questions to ensure that patients continue to understand the need to use contraception, as all four of these drugs can cause serious birth defects if a patient becomes pregnant before, during, or immediately after treatment.

3.5.1 Verification of Benefit and Treatment Maintenance Forms

Certain REMS drugs carry serious risks that are difficult to predict or prevent, and may cause irreversible harm to the patient. In these cases, it is important for patients and prescribers to regularly assess the benefit of the drug to ensure that it continues to justify the ongoing risk. Certain REMS include special treatment maintenance forms that prescribers and patients must complete to verify that the patient continues to benefit from the drug and has not experienced any adverse effects.

Examples:

- Sabril: Treatment Maintenance Form
- Tysabri: 12 Week Questionnaire
- Tysabri: Patient Status Report and Questionnaire.

3.5.2 *Patient Monitoring and Monitoring Forms*

A number of REMS require regular monitoring of patients, such as laboratory tests and periodic assessments by healthcare providers. In some cases, the monitoring may be documented using special monitoring forms. In other REMS, prescribers record the results of the monitoring and share the findings with the sponsor over the phone or using a website. Other REMS require that pharmacists confirm with the prescriber that monitoring has taken place before dispensing the drug.

Key Features of Patient Monitoring and Monitoring Forms:

- **Frequency of Monitoring**: The frequency of the required REMS monitoring depends on a number of factors, including the purpose of the monitoring and the consequences of failing to monitor frequently.
- **Timing of monitoring**: Monitoring may occur at a range of times during the medication use process, depending on who is doing the monitoring (e.g., the prescriber, the dispenser, etc.), when adverse events are most likely to occur (e.g., immediately after administration of the drug) and when the information from monitoring is most likely to be useful (e.g., before a drug is dispensed to help determine whether therapy needs to be stopped).

EXAMPLES

- Sabril: Ophthalmologic Assessment Form,
- Versacloz: WBC Count and ANC Monitoring Forms,
- Tysabri: Pre-Infusion Patient Checklist

3.5.3 *Verification of Safe Use Conditions*

In REMS, dispensers are frequently called upon to verify that safe use conditions are in place before dispensing the drug. For example, a dispenser may be asked to verify that the prescriber of the drug is enrolled and trained, that the patient has been enrolled and/or counseled, and that any necessary screening or monitoring have been completed.

The methods used to verify that safe use conditions are in place may depend in part on the setting in which the drug is typically used. When drugs are prescribed and dispensed in the same setting, the setting may be responsible for setting up a system to ensure that the drug is only dispensed when certain safe use conditions are in place.

When drugs are prescribed and dispensed in separate settings, a more standardized process is usually put in place to ensure that dispensers are able to verify safe use conditions that may have been carried out by a number of different healthcare providers. In some cases, the sponsor may take responsibility for tracking whether safe use conditions have been met: The healthcare providers who are responsible for carrying out safe use conditions report doing so to the sponsor, and those who dispense the drug are required to obtain "dispensing authorization" from the sponsor before dispensing the drug.

Key Features of Verification of Safe Use Conditions:

- **Authorization Numbers**: In many REMS, prescribers who complete REMS requirements for a particular prescription will receive an "authorization number" from the prescriber. By submitting that authorization number to the dispenser, they document that safe use conditions have been met. The dispenser then verifies with the sponsor that the authorization number is valid before dispensing the drug.

- **Prescription Order Forms**: Some REMS ask dispensers to fill prescriptions only after verifying they have been entered into a prescription order form, monitoring form, or other documentation of patient monitoring.
- **Electronic Verification of Safe Use Conditions**: More recently, REMS have begun to conduct dispensing authorizations in retail pharmacies using existing pharmacy management systems, the computer systems that retail pharmacists use in their day-to-day practice. These systems use the existing systems used to process third party prescription claims in order to automatically verify safe use conditions. They may also allow for the inclusion of "hard stops" in the pharmacy system to prevent unauthorized dispensing.

Examples:

- In iPLEDGE, pharmacists must go to the iPLEDGE website and obtain a special "Risk Management Authorization" number, which confirms that the prescriber is certified and that the patient has answered contraception questions and received a negative pregnancy test.
- In the Lotronex REMS, certified prescribers are asked to place a sticker on all Lotronex prescriptions, and pharmacists are then asked to check for these stickers on the prescription to make sure that the drug was prescribed by a certified prescriber. At a July 10, 2013 meeting of the Drug Safety and Risk Management Advisory Committee, the committee voted in favor of replacing this program, expressing concerns that it was incompatible with electronic prescriptions and was not integrated into pharmacists' typical workflow.
- In the TIRF REMS, retail pharmacies' pharmacy systems automatically check with a sponsor database before being permitted to dispense.
- Dispensers of Juxtapid and Kynamro may only dispense new prescriptions after receiving a "Prescription Authorization Form".

3.5.4 Tools for Managing Care Transitions

Most REMS focus on the healthcare providers who typically prescribe, dispense, and administer the drug. However, patients may be treated by a range of other healthcare providers, many of whom may have a role to play in mitigating the risk of a drug.

One transition of concern is the movement of patients into inpatient facilities, which can occur at any time while the drug is being used. REMS have introduced tools and approaches to address risks during this transition. For example, Soliris and Extraneal's REMS include special tools for patients to use to inform their care providers of these risks and how to address them. Soliris includes a patient safety card with information for hospital staff on the risk of infection in Soliris patients, and Extraneal includes a patient kit with letters and reminders to ensure that hospital staff are aware of the potential for falsely elevated blood glucose readings in Extraneal patients.

Examples:

- Soliris: Patient Safety Card
- Extraneal: Patient Kit

3.6 Adverse Event Reporting

REMS may seek to collect information on adverse events to support their risk mitigation effort and facilitate the assessment and improvement of the REMS. When healthcare providers enroll in the REMS, they will often agree to report any incidents of adverse events to the sponsor. Some REMS provide adverse event reporting forms and procedures to help collect detailed information on adverse

events of interest and the circumstances surrounding them. In some cases, these forms and procedures are associated with a patient registry.

3.6.1 Patient Registries for Adverse Event Reporting

As part of a REMS, patient registries may record adverse events. Patient registries are most frequently found in REMS for drugs that cause birth defects. For these products, a registry may be used to track patients who become pregnant and the outcome of the pregnancy.

Examples:

- Thalomid: Pregnancy Exposure Registry Protocol

3.6.2 Adverse Event Reporting Forms

As part of a REMS program, adverse event reporting forms may be used to collect information on specific adverse events of interest. Use of these forms allows the sponsor to collect more detailed information on a greater number of cases than might be obtained through spontaneous adverse event reporting.

Examples:

- Tysabri: Patient Discontinuation Questionnaire
- Zyprexa Relprevv: Post-Injection Delirium/Sedation Syndrome Form

3.7 Distribution Controls

In order to ensure that only certified healthcare providers who dispense REMS drugs receive the drugs to dispense, REMS programs often take steps to control the distribution of the drug. Some REMS limit distribution of the drug by requiring distributors to enroll in the REMS or sign a contract with the manufacturer assuring they will ship only to certified parties.

3.7.1 Distributor Enrollment Forms

When REMS drugs are distributed through normal distribution channels to retail pharmacies, the REMS may require distributors to enroll in the REMS using an enrollment form. The process for distributor enrollment is similar to that for other REMS stakeholders: As part of the enrollment process, distributors are required to provide basic information about their facilities, and sign a series of acknowledgments and agreements, including an agreement to ship product only to certified parties.

Examples:

- Adasuve: Wholesaler/Distributor Enrollment Form
- Isotretinoin: Wholesaler Agreement
- TIRF: Wholesaler / Distributor Enrollment Form

4 REMS Evaluation

4.1 Current Methods for Assessing REMS

FDAAA requires that REMS assessments be completed to determine whether a REMS is meeting its goals or whether the goal or elements should be modfied. These assessments are to be completed at least at 18 months, 3 years and 7 years after REMS approval. The REMS goals that are assessed focus on the risks that were identified when determining the need for a REMS. The specific REMS goals vary with the drug, but almost all REMS include a goal to inform prescribers and usually patients about the relevant risks. REMS with ETASU may have additional goals that focus on minimizing certain risks (e.g., teratogenicity, myocardial infarction), limiting use to certified prescribers or certain patients, or ensuring compliance with certain testing.

At the time of the approval of a REMS the Agency also includes an assessment plan for the Sponsor to follow. The complexity of the assessment plans depend on the complexity of the REMS. REMS with Communication Plan (CP) and/or Medication Guide (MG) require Knowledge, Attitude and Behavior (KAB) surveys that measure 1) prescriber and patient knowledge and understanding of serious risks and safe use conditions, and/or 2) prescriber knowledge of proper patient selection. The methodology for the KAB surveys utilized to assess REMS has not been standardized and was the focus of a workshop in June 2012.[10] That workshop included discussion about the validity and salience of KAB surveys and alternatives to surveys for assessing knowledge.

REMS with ETASU generally have additional metrics included in the assessment plan. Information about various processes is collected. The assessment plan can include data on compliance with REMS implementation requirements, such as the number of enrolled/certified prescribers, patients, pharmacies; the number of prescriptions by non-enrolled prescriber; the number of Dear Healthcare Provider letters mailed, and any corrective actions taken to address non-compliance. Data that summarizes compliance with certain safe use conditions may also be collected, such as the number of times patients have not completed required laboratory testing; the number of pre-infusion patient checklists received that suggest a patient should not be treated; and the findings from any Root Cause Analyses (RCA) (e.g., reasons for pregnancy).

Other metrics included in many REMS assessments relate to 1) utilization patterns – demographics of patients and prescribers, use in "at risk" populations (e.g., females of reproductive potential), and prescribing behaviors; and 2) patient outcomes – the number or rate of adverse events that the REMS is attempting to either mitigate (e.g., the number of pregnancies) or detect (e.g., PML).

At this time many of the REMS assessment metrics focus on processes and not outcomes of the REMS. Outcome-related metrics are challenging because there are usually no pre-REMS data or other good comparator data; outcomes (numerator) are often rare events; and drug use (denominator) may be limited. Measures of behaviors that might be indicators of success or failures, such as use of contraceptive while taking a teratogen, or determining whether patients were counseled, can also be difficult to obtain. Proxy measures, such as KAB survey findings, have been used to help determine if certain REMS goals have been met, but determining valid proxy measures is challenging.

As required under FDAAA, the Agency has convened three Drug Safety and Risk Management (DSaRM) Advisory Committee (ACs) since 2011 to discuss REMS with ETASU to determine if they: (1)

[10] June 7, 2012: Social Science Methodology Workshop: http://www.fda.gov/Drugs/NewsEvents/ucm292337.htm

are assuring safe use of the drug, (2) are not unduly burdensome on patient access to the drug, and (3) to the extent practicable, minimize the burden on the healthcare delivery system. The REMS that have been discussed include isotretinoin (2011), the REMS for teratogens with ETASU (2012), and alosetron (Lotronex) (2013). These meetings have included discussions about the challenges of assessing the effectiveness of REMS. The AC members have acknowledged the difficulties in assessing REMS, but have emphasized the importance of developing better metrics.

In addition to a discussion of suggested metrics that might be used to address the challenges mentioned above, Section III-E of the Federal Register announcement[11] lists three important questions that address REMS-related issues that the Agency would like the public to address. First, the assessment of patient and prescriber burden and access to a drug with a REMS are important parts of the overall evaluation of a REMS, but the methodology that might be used to obtain an unbiased determination of these concerns has not been developed – the Agency is looking for feedback. Secondly, for many REMS that are implemented, there are often other risk management activities occurring in parallel, e.g. advisory committee meetings, media coverage, etc. The Agency would like feedback on how to separate the impact of a REMS programs from these related activities. Lastly, determining the evidence needed to modify or release a REMS and still ensure the safe use of a drug is an important discussion—one that would help guide the Agency as it moves forward.

4.2 FDA's Approach to Building a Future REMS Assessment Framework and Guidance

The methods that have historically been used to assess the impact of pharmaceutical risk management programs have been the subject of both scrutiny and quality improvement efforts among legislators, regulators, stakeholders and auditors. While some efforts have been made to better understand the limitations of existing methods and to implement incremental improvements upon them (e.g., improving the design and implementation of knowledge surveys), a more comprehensive analysis of alternative methodology(s) to produce more meaningful information about the impact of risk management program has only recently been initiated. The factors influencing the need for making improvements to REMS assessments, the principles for evolving an improved methodology, a potential REMS assessment framework and, ultimately, the evolution of industry guidance will now be described.

4.2.1 Factors Driving the Need for Improved REMS Assessment Methodologies

Four key factors underlie the impetus to improve upon previous methods for assessing REMS programs: legislation, agreements between industry and FDA, feedback received from various stakeholders, and consistency with the efforts of other regulatory authorities.

FDAAA[12] gave FDA the authority to require and enforce the assessment of effectiveness of Risk Evaluation and Mitigation Strategies (REMS). A minimum requirement for a REMS program is to provide a timetable for assessment, and, as noted above, with a minimum assessment frequency of 18 months, 3 years, and 7 years. These assessments have most often been comprised of surveys of knowledge directed to prescribers, patients and/or pharmacists and/ measuring manufacturer and stakeholder compliance with requirements of ETASU. Less often, assessments of frequency/severity of the clinical safety outcome(s) of interest and root causes of program underperformance have been

[11] *Supra*, note 5

[12] *Supra*, note 1

conducted. These "domains" of assessment are determined based on the type(s) of REMS element(s) that comprise the risk management program.

In 2012, the FDA Safety and Innovation Act (FDASIA)[13] was signed into law. FDA's authority regarding REMS assessments was maintained and, when considering a REMS modification, the importance of assessing both the benefit and burden of the REMS program on the healthcare delivery system was added. Hence, there is a legislative imperative to include additional assessment domains.

The fifth Prescription Drug User Fee Act, authorized by FDASIA in 2012, included a mutually agreed upon set of goals between the pharmaceutical industry and FDA.[14] Among them was a goal for improving how assessments of REMS programs would be conducted. It states:

> "Measure the Effectiveness of REMS and Standardize and Better Integrate REMS into the Healthcare System", with two specific milestones:
>
> 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

As part of the Agency's efforts towards continuous quality improvement, and in anticipation of forthcoming legislation, FDA implemented 3 working groups in 2011, overseen by the REMS Integration Steering Committee, to better clarify and issue guidance on the criteria for requiring a REMS, standardization of REMS tools and the evaluation of REMS program effectiveness. The latter working group has implemented an effort to better understand alternative methodologies for REMS assessment, including developing a REMS assessment framework and, based upon that framework, to develop and publish draft guidance.

FDA had previously sought stakeholder feedback on assessing knowledge of risks using social science methodologies like surveys, in 2012. At that meeting, "Social Science Methodologies to Assess Goals Related to Knowledge" pharmaceutical industry presentations included a number of specific recommendations for assessing outcomes other than knowledge by using other methods.[15] Presenters cited the need for consensus on key outcomes to be measured as part of REMS assessments, such as exposure, useful/acceptability of information, navigability, comprehension, knowledge, self-efficacy, behavioral intent and actual behavior. Industry presenters also suggested employing additional data collection options: drug utilization studies, patient registries, secondary data sources and patient web-based communities.

Additional feedback about REMS assessments has come in the form of a January 2013 report, "FDA Lacks Comprehensive Data to Determine Whether REMS Improve Drug Safety," issued by the Office of

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[13] *Supra*, note 7

[14] PDUFA Reauthorization Performance Goals and Procedures FY 2013-2017: www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf April, 2012

[15] Industry Experience in Using Surveys to Assess REMS Impact on Knowledge presentation www.fda.gov/downloads/Drugs/NewsEvents/UCM307706.pdf June 7, 2012

Inspector General (OIG), based on an audit that was completed in 2012.[16] Among the seven major recommendations from that report, one was to "develop and implement a plan to identify, develop, validate and assess REMS components." Most relevant to the area of REMS assessment were that FDA should:

- Identify and implement reliable methods to assess the effectiveness of REMS.
- Decrease its reliance on survey data in sponsors' assessments and work with sponsors and health care providers to develop more accurate evaluation methods.
- Continue to hold discussions with stakeholders…about the issues and challenges associated with assessing the effectiveness of REMS components.

In the context of these factors, FDA has been seeking feedback from stakeholders and continues to do so in this public meeting.[17]

Recently, the European Medicines Agency published its draft guidelines on Good Pharmacovigilance Practices. Module XVI of that guidance discusses proposed assessment domains for risk management programs that are implemented in the EU. These regulators proposed extending the domains of assessment of such programs to include:

1. Process measures - extent program has been executed and intended impacts on behavior achieved, such as reaching target population, assessing clinical knowledge and assessing clinical actions (drug utilization studies)
2. Outcomes measures – measure of level of risk control, such as the frequency and severity (pre-post or observed vs. expected epidemiology studies).

Additionally, the EMA suggested measuring unintended outcomes.

4.2.2 Principles Guiding the Development a REMS Assessment Framework

As FDA researches and reviews alternative methodologies to identify a more robust REMS assessment framework and use it as the basis for developing guidance, the Agency needs to consider some guiding principles to help prioritize and ensure that the method(s) that is/are chosen will both address the aforementioned factors and generate more meaningful, actionable information.

Three guiding principles are considered vital in this regard, although others may also need to be considered:

1. Learn from and retain best practices from how REMS assessments have been conducted in the past. The use of knowledge surveys has been refined over time and, although they

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[16] DHHS OIG Report: FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety, February 2013, https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf.

[17] Standardizing and Evaluating Risk Evaluation and Mitigation Strategies; Notice of Public Meeting; Request for Comments www.gpo.gov/fdsys/pkg/FR-2013-05-22/pdf/2013-12124.pdf Federal Register, Vol. 75, No. 116, Thursday, June 17, 2010, Notices.

remain flawed, they do provide information about how well stakeholders understand serious risks and their understanding of their role in achieving the goals of a REMS.

2. Select a robust, comprehensive and evidenced-based approach, optimally one that has a basis in science, with supportive literature about its effectiveness. A methodology consistent with the scientific method, that is comprehensive in nature and has the potential to evolve into a science on par with that used in pharmacoepidemiology, would be ideal in this regard.

3. Consider the practical feasibility and utility of any method(s) selected. There is little value to defining solution(s) that end up being too difficult or costly to implement and/or that will not provide actionable information. Pre-testing of selected method(s) for their utility in enhancing existing REMS assessment plans will help to validate the selected method.

4.2.3 REMS Assessment Framework Options and Feasibility

In seeking a framework for measuring the impact of healthcare interventions that addresses the aforementioned factors and that also retains best practices, has a basis in science, and is practical to implement, a number of diverse frameworks could be considered.

One framework for measuring the impact of a learning program is the Kirkpatrick Four Level Evaluation Model.[18] This Model's four steps of evaluation consist of:

1. Reaction – how well did the learners like the process?
2. Learning – what did they learn (gain knowledge and skills)?
3. Behavior – what changes resulted from the learning process?
4. Results – what are the tangible results of the learning process?

Another framework, from the implementation sciences, RE-AIM (an acronym for the framework's functional elements) was developed in 1999[19] for purposes of assessing the public health impact of an intervention as a function of five factors:

1. Reach – the proportion of the target population who participate
2. Effectiveness – success rate (positive – negative outcomes)
3. Adoption – proportion of settings that adopt the intervention
4. Implementation – extent to which intervention is implemented as intended
5. Maintenance – extent to which intervention is sustained over time

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[18] Techniques for evaluating training programs. Kirkpatrick, DL et. al., *Journal of American Society of Training Directors*, 13 (3): 1959; pp21–26.

[19] Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Glasgow, et.al. *Am. J. Public Health*, Sept. 1999, Vol. 89, No. 9.

The product of these five dimensions is the public impact score.

Various industries have also employed failure analysis methods [20] to either predict and/or retrospectively assess behavioral causes of process failures and the impact of programs designed to mitigate them. While not as comprehensive as the aforementioned options, an assessment framework that could systematically identify and measure the behavioral causes of process failures would help improve our understanding of the impact of healthcare intervention programs, as well as how to improve their design.

To determine the feasibility of using an existing framework to improve REMS assessment methods, FDA envisioned a broad spectrum of possible REMS assessment domains, ranging from program implementation processes and distribution metrics through knowledge and behavior adoption/compliance to clinical outcomes and underlying causes of program failure. The additional measurement domains of particular legislative and industry interest, program burden and impact on patient access, were also incorporated.

As an example, these various domains were aligned with the RE-AIM categories of reach, effectiveness, adoption, implementation and maintenance. RE-AIM was selected as it appeared to fit best with the spectrum of domains envisioned, had extensive evidence of application to public health intervention research,[21] and was readily adaptable. Remarkable alignment was achieved between the RE-AIM categories and the spectrum of possible REMS assessment domains, as depicted below.

Category	Possible REMS Assessment Domains
Reach	Distribution/Availability/Receipt Participation Medication access
Effectiveness	Knowledge: awareness/comprehension/understanding 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

[20] DeRosier J, Stalhandske E, Bagian JP, Nudell T. Using health care failure mode and effect analysis: the VA National Center for Patient Safety's prospective risk analysis system. *Jt Comm J Qual Improv*. 2002 May;28(5):248-67,209. http://www.patientsafety.va.gov/SafetyTopics/HFMEA/HFMEA_JQI.pdf

[21] www.re-aim.org

	Consistency Burden
Maintenance	Persistency Failures

Extending this framework to also consider standardized REMS tools (program overall, communication plan (CP), ETASUs A through E), as well as future ones, there is an opportunity to specify a standard set of assessment domains specific to each type of REMS tool. For each domain, the numerator and denominator used to calculate the value will also need to be defined, along with, possibly, threshold values.

Category	Possible REMS Assessment Domains	Metrics (overall REMS)	Metrics (specific tools)
Reach	Distribution / Availability / Receipt Participation Medication access	Numerators / Denominators	Numerators / Denominators
Effectiveness	Knowledge Outcomes Unintended effects	Numerators / Denominators	Numerators / Denominators
Adoption	Application of knowledge Attitude/intention Behaviors	Numerators / Denominators	Numerators / Denominators
Implementation	Process Consistency Burden	Numerators / Denominators	Numerators / Denominators
Maintenance	Persistency Failures	Numerators / Denominators	Numerators / Denominators

Finally, the relevant data collection system or data source for each assessment domain needs to be identified, thereby helping to confirm the feasibility of generating the desired information for each domain. REMS assessments may incorporate a spectrum of data systems/sources, including REMS program data, epidemiological studies, drug utilization data, patient registries, surveys, market research, audits, enhanced pharmacovigilance, failure mode and effects analysis (FMEA), root cause analysis (RCA), ethnographic research, and more.

4.2.4 REMS Assessment Guidance Development

Although yet to be validated, building a REMS assessment framework that addresses the identified factors and follows the predefined principles appears to be feasible. It will ideally be based on an existing healthcare intervention assessment framework like RE-AIMS. The framework should address all possible assessment domains, specify a standard set of metrics for each REMS tool and define the relevant data systems/sources of the information for each. As such, it creates a rational basis for evolving guidance for industry on the assessment of REMS programs.

The process of guidance development is underway. It will also need to specify the composition of assessment plans, study protocol and analytical methodologies, the viability of establishing performance thresholds, and the limitations of the selected methodology(s).