

Strengthening Risk Evaluation and Mitigation Strategies (REMS) Through Systematic Analysis. Standardized Design. and Evidence-Based Assessment

Background

With the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, Congress authorized the U.S. Food and Drug Administration (FDA) to require Risk Evaluation and Mitigation Strategies (REMS) to assure that the benefits of a drug or biologic product outweigh the risks. REMS accomplishes the important functions of mitigating potential hazards associated with the use of certain drugs, and helping to ensure the safe use of medical products through a variety of risk minimization tools and procedures. With REMS in place, FDA has been able to facilitate access to a host of drugs that may have otherwise not have been approved and allow products to remain on the market with greater confidence.¹ However, concerns have arisen regarding the effects REMS programs have on patient access to medications and potential burden on the health care system. In response to these concerns, FDA has initiated programs aimed at improving the standardization, integration and assessment, of REMS within the health care system. In particular, FDA launched the REMS Integration Initiative in 2011 to clarify how statutory criteria is used to determine whether a REMS is necessary, establish best practices in the design and implementation of REMS and develop evidence-based evaluation methodologies for assessing the effectiveness and burden of REMS. Moreover, FDA has made a series of commitments aimed at enhancing REMS by ensuring their development in consultation with drug industry representatives, patient and consumer advocates, and health care professionals. These and other commitments were incorporated into the reauthorization of the Prescription Drug User Fee Act (PDUFA), a component of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012.

Elements of REMS Programs

REMS programs use a diverse set of risk minimization strategies, or REMS “tools”, to mitigate a serious risk associated with a particular drug. Generally, REMS tools are designed to inform prescribers, pharmacists, and/or patients of these risks, and educate or train them and/or ensure awareness or implementation of any necessary procedures/testing to mitigate them. Approved REMS programs typically include one or more of the following components:

- 1) Medication Guide or Patient Package Insert (PPI)
 - FDA-approved patient labeling to inform and optimize patient treatment.
- 2) Communication Plan
 - Risk communications (e.g., Dear Healthcare Provider letters) to healthcare providers, such as physicians, pharmacists, nurses, and physician assistants.
- 3) Elements to Assure Safe Use (ETASU)
 - Prescribers have specific training/experience or special certifications;
 - Pharmacies, practitioners or healthcare settings that dispense the drug be specially certified;

¹ Strom, B. L. (2012) *Pharmacoepidemiology*, Fifth Edition (eds B. L. Strom, S. E. Kimmel and S. Hennessy), Wiley-Blackwell, Oxford, UK. (p.522) doi: 10.1002/9781119959946.ch1

- Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals);
 - Drug be dispensed with evidence of safe-use conditions such as laboratory test results;
 - Each patient using the drug be subject to monitoring; and
 - Each patient using the drug be enrolled in a registry.
- 4) Implementation system
- System to monitor and evaluate implementation of Elements to Assure Safe Use.

Development and Approval of REMS Programs

If FDA determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks, product “sponsors” (i.e., biopharmaceutical manufacturers) may be required to submit a proposed REMS document as part of new drug applications (NDAs), abbreviated new drug applications (ANDAs), or biologic license applications (BLAs). Sponsors can also be required to submit a proposed REMS after the approval of a drug, if FDA becomes aware of new safety information and determines that a REMS is necessary (e.g., through postmarket safety studies).

Generally, sponsors propose a REMS design that is reviewed by, and adapted in consultation with, FDA. The need for a REMS and the required REMS elements is decided among review divisions within FDA after taking into account statutory requirements, external Advisory Committee opinion, the perceived intrinsic ability of the healthcare system to effectively manage the risk, the potential burden the REMS may impose on the healthcare system, previous REMS program designs and other considerations. Once a sponsor’s proposal is approved, the sponsor is then responsible for implementing the REMS.

While approximately 200 REMS have been approved since 2008, FDA has since released many REMS programs composed of medication guides only.² As of September 2013, 70 REMS programs remain in effect, with 64 of these REMS designed and approved for individual drugs and 6 REMS as shared systems between multiple products.³ Shared system REMS can be applied to an entire class of products, such as the approved REMS for extended-release and long-acting opioid analgesics.⁴

Implementation of REMS Programs

The implementation of a REMS program is the responsibility of the individual sponsor, based on specifications agreed upon between the sponsor and FDA as described in the proposed REMS document. Sponsors provide materials, forms, website content and/or support services to healthcare providers and pharmacists who, in turn, are responsible for implementing the REMS in their respective setting, as well as communicating risk information to patients. Risk information to patients may also be conveyed directly by the sponsor.

For REMS programs which include a Communication Plan, product sponsors disseminate information to health care providers to encourage implementation and explain certain safety protocols. Product sponsors may work with health care provider professional societies and other stakeholders to further support the implementation of a REMS program. For REMS programs which include Medications Guide,

² U.S. Food and Drug Administration. Guidance Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). Accessed September 4, 2013. Retrieved from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm244570.pdf>

³ U.S. Food and Drug Administration, Approved Risk Evaluation and Mitigation Strategies (REMS). Accessed September 9, 2013. Retrieved from: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm>

⁴ Ibid.

sponsors work with pharmacies, practitioners, or health care settings to ensure that the approved information is dispensed with the drug or biological product.⁵

The implementation process for REMS programs with ETASUs can vary greatly depending on the scope and scale of each component. In REMS which require certification of healthcare providers, programs must be able to certify that health care professionals have adequate knowledge of educational materials, risk of drug, and conditions of safe use, as well as the ability to diagnose and treat potential adverse reactions. ETASUs which require certification of those who dispense may require similar certification processes and training. ETASUs may require the implementation of patient registries, patient monitoring services (e.g., blood test, questionnaire), or other documentation requirements. Additionally, for REMS programs which restrict distribution, sponsors must work with stakeholders to ensure that the drug is dispensed to patients only in approved health care settings.⁶

Assessment of REMS Programs

The assessment of a REMS is essential to ensure that the program is successful in achieving its goals and effectively mitigating the known risks of a drug. In order to ensure that REMS programs are regularly reviewed, sponsors are required to submit REMS assessments at standard intervals throughout a drug's lifecycle. At the time a REMS submission is approved, FDA provides a timetable for when the program will be evaluated to determine if it has met its intended goals and/or whether a goal or element should be modified. These assessments are conducted at least at 18 months, 3 years, and 7 years after REMS approval.⁷ A sponsor may additionally submit a voluntary assessment or propose modifications to an approved REMS at any time.

FDA works with sponsors to develop an assessment plan as part of the initial REMS approval process. The assessment plan describes the information that FDA requests sponsors collect in order to assess whether a REMS is meeting its goals. The specific requirements for assessments can vary depending on the unique components of a REMS program.

Drug sponsors are typically responsible for developing methods to assess their REMS programs. Once a periodic assessment of a REMS program is completed by the sponsor, an assessment report is then submitted to FDA for review. In response to this submission, FDA produces a memorandum document which contains FDA's review of the sponsor's assessment report. FDA may request that sponsors conduct an additional assessment as a basis for determining whether the REMS should be modified.

Current Issues in REMS Design, Implementation, and Assessment

If appropriately designed, implemented, and assessed, REMS programs have the potential to make important drugs accessible to patients while minimizing serious adverse effects. However, inconsistency and lack of standards in current approaches to the design, implementation, and assessment of REMS can result in potentially inefficient and less effective REMS programs.

⁵ U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategies (REMS). Accessed September 13, 2013. Retrieved from: <http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM276838.pdf>

⁶ Ibid.

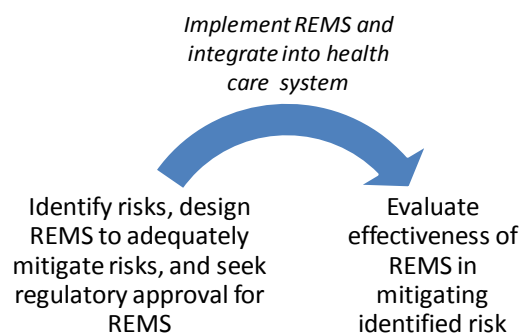
⁷ U.S. Food and Drug Administration. Draft Guidance: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. Accessed September 4, 2013. Retrieved from: <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>

Once the potential for a specific drug-related adverse outcome has been identified, and FDA has concluded that intervention beyond labeling is necessary to mitigate the risk, a series of important determinations need to be made. First, the determination must be made that existing health care systems lacks adequate expertise, resources, or coordination to effectively mitigate the risk. If it is determined that the existing health care system cannot adequately mitigate the risk of an adverse event, then a REMS program may be required.

Generally, the process for the designing and implementing a REMS program (illustrated in Figure 1) involves:

- 1) Identification of conditions of unsafe use or healthcare system failures that may increase the risk of an adverse event associated with the drug;
- 2) Development and implementation of strategies to mitigate those conditions or failures; and
- 3) Evaluation of REMS program effectiveness and the need for program modification.

Figure 1: Current REMS Design and Assessment



To date, lack of consistency and standardization within each of these steps has presented significant challenges for regulated industry, regulators, health care providers, and other stakeholders.

Inconsistency and Variation in REMS Design and Development

Unnecessary and excessive variation in REMS program design poses a significant problem for drug sponsors, regulators, and health care providers. Differences in factors including the type of risk, context of care, and sponsor expertise and resources, can lead to significant variation in REMS design. While some variation is appropriate given that REMS must be tailored to address the unique risk-benefit profile of each drug, similar risks should be consistently and reliably identified, characterized and mitigated in a relatively similar manner.

Lack of standardization in the REMS design process can present a significant problem for a host of reasons. REMS design is a complex and resource intensive process that has significant implications for the development of a drug and the timely approval of a drug application. As such, inconsistency or unpredictability in the design process can impose significant costs and delays. Sponsors need to be able to anticipate the costs and time needed to design, document and develop a REMS program, and regulators would benefit from having a streamlined and consistent approach to reviewing and approving REMS programs. Furthermore, variations within REMS programs can also stem from a failure to identify, replicate and adopt best practices. This can result in unnecessary variations between REMS programs for drugs with similar risks and/or contexts of care. These inconsistent REMS programs also present an implementation burden for health care providers, who must adapt when these REMS programs are integrated into workflow processes.⁸

⁸ U.S. Food and Drug Administration. FDA Presentations at REMS Public Meeting, July 25-26, 2013. Accessed September 10, 2013. Retrieved from: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM363676.pdf>

Inadequate Evaluation of REMS Program Effectiveness

These variations in the design, development and implementation of REMS, as well as inconsistencies in methods to assess REMS programs' effectiveness, have made the assessment of REMS a challenge. Recent findings from a report from the Office of Inspector General (OIG) indicate that FDA does not have comprehensive data from sponsors to adequately assess whether the REMS tools are meeting their goals.⁹ Among the REMS assessments reviewed by OIG, nearly half lacked the information requested by FDA in their assessment plan. Moreover, in several instances FDA could not determine whether REMS were meeting their goals as a result of the incomplete information in assessments submitted by sponsors (e.g., lack of assessment of patients' understanding of risks).

Issues have also been raised regarding the collection of information needed for the assessment of REMS programs. For instance, REMS that incorporate communication plans and/or Medication Guides are typically assessed through Knowledge, Attitude, and Behavior (KAB) surveys. These surveys measure prescriber's and patient's knowledge and understanding of serious risks and safe use conditions, and/or a prescriber's knowledge of proper patient selection. Concerns have arisen regarding patient confidentiality and a lack of standardized format, issues which may contribute to low levels of survey completion. In addition, stakeholders have raised issues regarding insufficient sample sizes, potential bias through convenience samples, unrepresentative survey population demographics, and a lack of standards and uniform processes for conducting KAB surveys.¹⁰

REMS which include more restrictive components, such as those with ETASU, face additional challenges related to data collection and analysis. These REMS programs generally require that additional metrics be included in a sponsor's assessment, such as the number of enrolled prescribers, patients, pharmacies in a REMS program. Product sponsors may also collect information related to utilization patterns (e.g., use in "at risk" populations) and patient outcomes (e.g., rate of adverse event that the REMS is intended to mitigate). However, outcome-related metrics can present challenges during data collection and analysis, as many REMS products often have little to no pre-REMS data or equivalent drugs for comparison.¹¹

Future Efforts to Standardize REMS Programs

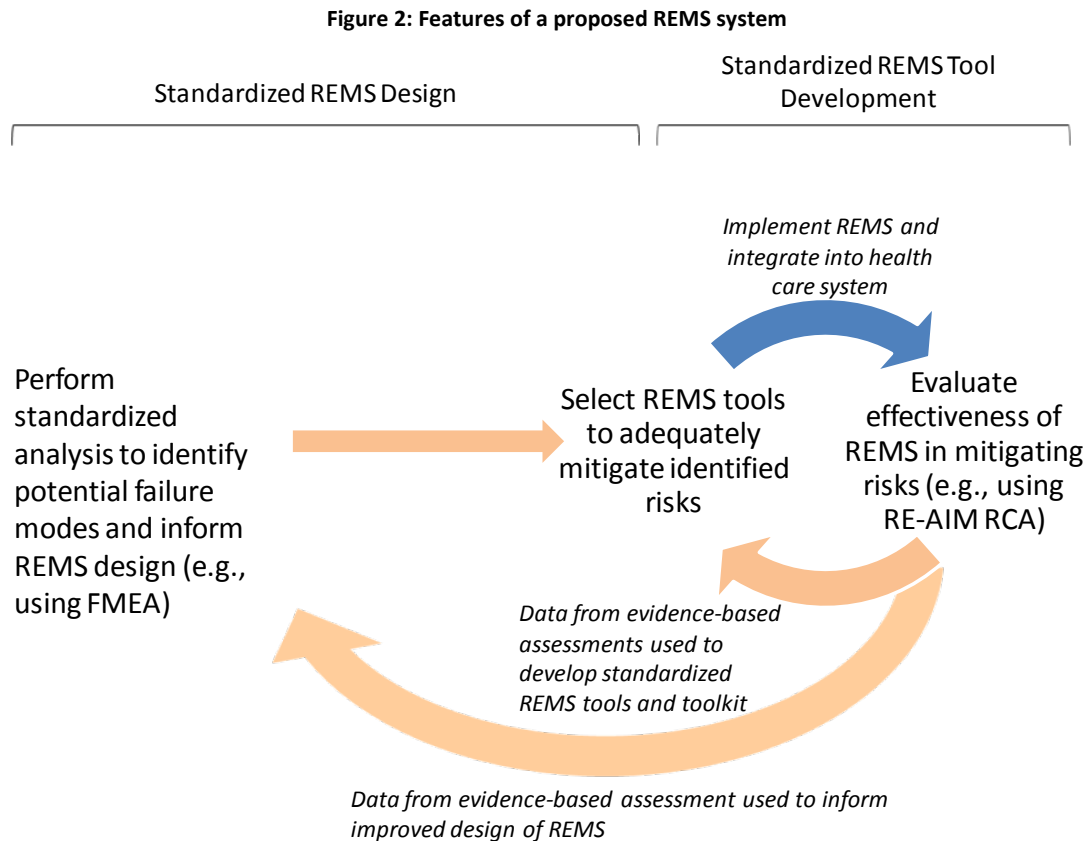
FDA and other relevant stakeholders have expressed concern that these variations and gaps may undermine the effectiveness of REMS and result in an increased burden on both the pharmaceutical industry and health care system. Minimization of unnecessary variation in REMS design and evaluation through greater standardization, including the adoption of systematic methods and processes as well as standardized tools, has the potential to increase the effectiveness of REMS programs as well as reduce uncertainty and burden on the health care system. More rigorous, comprehensive, and standardized approaches within each step in the REMS design, implementation, and assessment process can facilitate more consistent and reliable identification, characterization and mitigation of risks.

⁹ U.S. Department of Health and Human Services. Office of Inspector General (OIG). FDA Lacks Comprehensive Data to Determine Whether REMS Improve Drug Safety. Retrieved from: <https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf>

¹⁰ U.S. Food and Drug Administration. Issue paper: Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. June 7, 2012. Retrieved September 5, 2013 from: <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301966.pdf>

¹¹ U.S. Food and Drug Administration. Background Materials: REMS Standardization and Evaluation Public Meeting. Retrieved September 5, 2013, from: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM362078.pdf>

As previously described, generally, stakeholders proceed through several distinct stages of the REMS development pathway: Identification and characterization of the causes of drug-related adverse events, design, development and implementation of risk mitigation tools, and evaluation of REMS effectiveness. As illustrated in Figure 2, each of these steps in the process can achieve greater consistency, efficiency and effectiveness through standardization.



First, a consistent and transparent risk evaluation framework for sponsors could be developed to prospectively analyze potential failures by stakeholders involved in the medication use process that may increase the likelihood of an adverse event. Second, this framework could then serve as the foundation for standardizing REMS program design by informing and guiding sponsors in selecting REMS tools that will effectively target probable failures and their underlying causes. Finally, the framework could support systematic, retrospective evaluation of these REMS tools to determine the overall effectiveness of the REMS, the root causes of REMS program failures, and the steps (e.g., REMS modifications) that could be taken to improve future program effectiveness. The results of these standardized analyses and assessment methods should inform REMS design, as well as tool selection, development, implementation and program assessments.

Systematic Approaches to Initial Risk Identification, Characterization and Evaluation

A standardized approach to risk management can start with a framework for systematic, prospective identification and prioritization of failures within a given process that can lead to increased risk, and inform the design and development of risk mitigation tools. Other industries and professions have successfully employed systems engineering approaches to dramatically decrease risk and adequately mitigate failure. For example, systems-based risk mitigation and failure analysis tools have been

successfully implemented within the aerospace/aviation and nuclear engineering fields. The techniques and tools used could in turn inform the development of a standardized framework for REMS design and assessment.

There are several key characteristics of systematic frameworks for risk identification and prioritization that are important to consider in the context of drug safety. A systematic framework for risk identification and prioritization should be able to:

- Enable sponsors to systematically and prospectively identify and prioritize system or process failures that may lead to increased risk;
- Provide sponsors with the opportunity to identify possible failure modes that may have otherwise gone unnoticed; and
- Help sponsors clearly convey to regulators what risks were identified, which risks were being mitigated, the approach to mitigation, and the rationale for each of those decisions.

FMEA: A Potential Framework for Standardizing REMS Program Design

One leading framework for this type of analysis is Failure Mode and Effects Analysis (FMEA). FMEA is a formal and systematic approach that examines each basic hardware, software, personnel, or functional element of a system. FMEA is designed to identify when and how a system may fail, assess the relative effects of various failures, and help identify what areas that may need to be examined to prevent those failures from occurring.

The data is typically analyzed and documented using a worksheet that takes a team through a step-by-step process in which they list the specific steps involved in a particular process, list potential failure modes and their causes, and evaluate the relative severity of each identified failure mode (e.g., through assigning Risk Priority Numbers). The team can then use this information to plan interventions based on the prioritized list of failure modes.¹²

This approach has a number of advantages and limitations. One key advantage is that it is a “bottom up” process analysis technique for failure identification and subsequent risk assessment. It begins by asking the questions, “what happens if,” and then proceeds to enable users to identify all of the potential effects of that initial failure.¹³ Additionally, it facilitates the consideration of risks that would otherwise have remained undetected. Some of the potential drawbacks of FMEA is that it has largely been applied in the design and manufacturing settings and often relies on human performance to mitigate the effects of system failure. This poses a challenge for its application within REMS, as failures within REMS program can often be a result of human error.¹⁴

This type of analysis has been adapted and used in health care delivery settings (i.e., HFMEA), including assessment of the medication use process by the pharmaceutical industry (i.e., RxFMEA).^{8,15} Other types of analysis put forth include probabilistic risk assessment, fault tree analysis, and gap-analysis.

¹² Rep. Institute for Healthcare Improvement. (2004). Failure Modes and Effects Analysis (FMEA). Retrieved September 4, 2013 from: <http://www.ihi.org/knowledge/Pages/Tools/FailureModesandEffectsAnalysisTool.aspx>

¹³ Marx, D. A., and A. D. Slonim. (2003). Assessing Patient Safety Risk before the Injury Occurs: An Introduction to Sociotechnical Probabilistic Risk Modelling in Health Care. *Quality and Safety in Health Care* 12.90002: 33ii-38. Retrieved September 4, 2013 from: <http://www.ncbi.nlm.nih.gov/pubmed/14645893>

¹⁴ Berman, B. A. (November 2003). Expert Evaluation of RxFMEA: An Adaptation of Failure Modes and Effects Analysis for Pharmaceutical Risk Management. ParagonRx. Retrieved August 28, 2013 from: http://www.paragonrx.com/downloads/white_papers/Expert%20Evaluation%20of%20RxFMEA.pdf.

¹⁵ DeRosier J.M., Stalhandske E.J., Bagian J.P., Nudell T. (May 2002). Using Healthcare Failure Mode and

Development of a Standardized REMS Toolkit

A systematic framework can create more consistent and less burdensome processes for designing, selecting, and justifying which tools are most appropriate for a particular REMS program. Once the risks and system failures have been identified and prioritized, and responsible stakeholders have been defined, tools (e.g., medication guides, prescriber training) must then be designed and implemented. This process could be streamlined through the development of standardized REMS “toolkit”, a set of pre-designed tool “templates” that address the most common causes of failure by stakeholders, represent best practices and have been shown to be effective in helping ensure safe use conditions across a wide range of REMS programs. While standardized, each component must be able to accommodate unique adverse event risks, educational messages and counseling instructions associated with each drug or class of drugs. This REMS toolkit approach has the potential to decrease the burden on sponsors when designing a program and improve the efficiency of the design process.

Recently, FDA has launched efforts to systematically characterize the types of tools used within previous REMS programs. This process can serve to inform the development of a standardized REMS toolkit by categorizing the various REMS tools which are currently utilized in REMS programs. Categories of REMS tools identified by FDA include:

- *Communications to Healthcare Providers*
 - Dear healthcare provider letters, websites, journal information pieces
- *Training of Healthcare Providers*
 - Training materials, overviews, prescribing information
- *Enrollment and Certification of Healthcare Providers*
 - Prescriber and dispenser enrollment forms
- *Initiation of Therapy and Patient Counseling*
 - Patient-prescriber agreements, patient educational materials, medication guides, counseling tools
- *Ongoing Patient Care*
 - Patient monitoring, verification of safe use conditions
- *Adverse Event Reporting*
 - Patient registries, adverse event reporting forms
- *Distribution Controls*
 - Distributor enrollment forms⁹

Standardized REMS Program Assessment and Evaluation

Assessment of REMS programs is a critical component for achieving the overall objective of mitigating drug risks. These assessments can serve not only to evaluate overall REMS program effectiveness (e.g., meeting program goals), but can also provide information about implementation, knowledge, behaviors, compliance, and potentially, program burden. However, as described above, the recent report by the OIG showed that many of the current REMS evaluations lack effective and meaningful processes for data collection and assessment. It is likely that a more robust, standardized REMS assessment framework would likely help to support an effective REMS evaluation process.

Effect Analysis: The VA National Center for Patient Safety’s Prospective Risk Analysis System. *Journal on Quality Improvement*. Retrieved August 28, 2013 from: http://www.patientsafety.va.gov/SafetyTopics/HFMEA/HFMEA_JQI.pdf

A number of features have been identified by FDA to help ensure that this system serves as a rational basis for industry to assess REMS. Some of the features include the ability to:

- Address a broad spectrum of assessment domains;
- Specify a standard set of metrics for the overall program and each REMS tool; and
- Define the relevant data systems and/or sources of data.²

Potential Frameworks for Standardized REMS Program Evaluation

FDA, recognizing the need for such a system, is working to identify an appropriate framework for REMS evaluation. One possible framework to conduct such an assessment is “RE-AIM”. RE-AIM has been used to assess the public health impact of healthcare intervention programs by looking at five factors: reach, effectiveness, adoption, implementation, and maintenance. Measures associated with these five factors are then multiplied to determine the public impact score.¹⁶

This framework provides a number of advantages, including providing sponsors with a structured approach for measuring the effectiveness of a particular REMS. However, one potential limitation of RE-AIM is that it equally weighs each of the five factors, whereas in some situations differential weights may be more appropriate.¹⁷

Another potential framework for REMS assessment, which could complement or be incorporated into RE-AIM, is root cause analysis (RCA). RCA is a method of determining the initial causal factors leading to a particular outcome, in this case, reasons for program failure. The RCA process has been designed to provide answers for what occurred, why it occurred, and what can be done to prevent it from occurring again.^{18,19} RCA has been implemented in the health care setting (e.g., U.S. Department of Veterans Affairs) and has provided important infrastructure for identifying and understanding the causes of a particular failure. However, one drawback to current implementation of RCA is that once a root cause has been identified, little follow-on is done to ensure that the risk of re-occurrence has been mitigated.¹² Thus, a vital element of any effective REMS system will need to ensure that information from these analyses can inform future redesign, tool modification and reassessment of the revised REMS.

Meeting Objective and Discussion Questions

To further explore these issues, the Engelberg Center for Health Care Reform at the Brookings Institution, in cooperation with FDA, is holding an expert workshop to explore the standardization of the design, tools, and assessment of REMS. This workshop will provide a forum for a wide array of stakeholders, including FDA, manufacturers, healthcare providers, and key content area experts, to explore systematic processes for risk evaluation, implications for adopting standardized approaches in the development of REMS, potential standardization of REMS tool selection in instances where a common toolkit may be useful, and enhanced strategies to assess the effectiveness of REMS.

¹⁶ "Reach Effectiveness Adoption Implementation Maintenance (RE-AIM)." *RE-AIM*. VirginiaTech College of Agriculture and Life Sciences, n.d. Web. 05 Sept. 2013.

¹⁷ Glasgow, R. E., Vogt, T. M., & Boles, S. M. (1999). Evaluating the Public Health Impact of Health Promotion Interventions: The RE-AIM Framework. *American Journal Of Public Health*, 89(9), 1322-1327.

¹⁸ Wu, A. W., A. K. M. Lipshutz, and P. J. Pronovost. (2008) Effectiveness and Efficiency of Root Cause Analysis in Medicine. *JAMA: The Journal of the American Medical Association* 299.6: 685-87.

¹⁹ United States Department of Veterans Affairs. Department of Veterans Affairs National Center for Patient Safety: National Center for Patient Safety - Root Cause Analysis Tools. Retrieved September 5, 2013 from: <http://www.patientsafety.va.gov/CogAids/RCA/index.html>

This workshop will provide an opportunity for stakeholders to discuss the broad objectives, potential opportunities, and challenges associated with REMS standardization, as well as a series of potential frameworks for improving their design, tool selection, and assessment. To facilitate the conversation around these topics, the workshop is divided into three sessions in which a few lead discussants will start the conversation with brief remarks, followed by an open discussion among participants in the room. Prior to these sessions, representatives from FDA will provide an overview of the broad goals associated with efforts to strengthen REMS.

Session I: Exploring Systematic Approaches for Standardizing REMS Design

Rigorous, evidence-based approaches to risk identification, characterization, and prioritization have been employed successfully in a wide range of industries. These approaches have helped minimize risk by providing a structured and often quantitative method for systematically and prospectively analyzing the spectrum of potential failures in a particular system and their associated risks. This session will give participants the opportunity to understand these frameworks and examine potential modifications to adapt them to REMS design and development. The session will begin with a discussion of one leading framework, FMEA, and its applications in the healthcare delivery and medication use systems. Potential discussion questions may include the following:

- FMEA: A Potential Framework for Systematic Prospective Risk Identification, Evaluation, and Mitigation
 - What is Failure Mode and Effects Analysis (FMEA)?
 - How have systems engineering approaches been successfully applied to improve patient safety in health care (e.g., HFMEA, RxFMEA)?
- What are other systematic approaches that exist to prospectively identify, evaluate, and mitigate risks that can inform the design of REMS?
 - Risk Management Plans (i.e., European Medicines Agency)
 - Probabilistic Risk Assessment
 - Fault Tree Analysis (FTA)
 - Hazard Analysis and Critical Control Points (HACCP)
 - Gap Analysis
- What are the trade-offs between these different approaches? What are the specific benefits and weaknesses?
- How can these approaches be adapted to provide evidence-based design of REMS programs?
 - How can these approaches encourage comprehensive and systematic evaluation of failures or hazards?
 - How can these approaches evaluate probability and severity of drug safety risks?
 - How can these approaches be used to identify where interventions are needed and how many interventions are needed (i.e., redundancy)?
- What practical considerations should FDA be aware of while considering the adoption of a systematic approach to REMS design?

Session II: Practical Considerations for Applying Systematic Approaches to the Development of Standardized REMS Tools

In selecting and employing systematic approaches to risk identification, characterization, and prioritization, an important consideration will likely be how the framework selected could then be leveraged to inform the design and selection of specific REMS tools. In addition, although flexibility and some variation in REMS design are certainly necessary giving the unique combination of drug, set of

stakeholders, and settings, an opportunity may exist to standardize a set of similar tools used to mitigate like risks or common causes of failure. This session will allow participants to explore these possibilities and discuss some of the practical considerations that will need to be taken into account. Potential discussion questions may include the following:

- How can these systematic approaches be used to inform the design of specific REMS tools (e.g., communications, checklists)?
 - How can these approaches assist in specifying the timing, audience, format and content of tools?
 - Are there systematic approaches that can complement the approaches outlined in session I? How might these systematic approaches support the development of REMS tools?
- How can systematic approaches to the design of REMS be used to inform the development of a standardized REMS toolkit?
 - Are there lessons that can be drawn from these systematic approaches and applied across a wide range of REMS?
- How will the application of a prospective risk evaluation framework impact the development of REMS and REMS tools?
 - What are the needs of sponsors, regulators, and other relevant stakeholders?
 - How can various stakeholders be engaged in the design process?

Session III: Investigating Potential Mechanisms for Standardizing the Evaluation and Assessment of REMS

REMS assessments can play an important role in ensuring that the REMS program and the tools selected to mitigate particular risks meet their stated objectives. A more rigorous, standardized approach to REMS assessments could greatly enhance the ability of stakeholders to understand what REMS tools are most effective and use that information to inform future REMS design and tool selection processes. In identifying effective frameworks for the standardization of REMS assessments, a number of features will likely be important, including the ability to take in qualitative as well as quantitative data. During this session, participants will identify potential frameworks for consistent REMS assessment and explore potential mechanisms for incorporating this information into the REMS design pathway. Potential discussion questions may include the following:

- What systematic approaches exist to retrospectively identify and evaluate risks and failures, to inform the evaluation and improvement of REMS?
 - Root Cause Analysis (RCA)
 - Others?
- How can these retrospective approaches be aligned with the prospective approaches described earlier?
 - How can retrospective approaches be used to validate the assumptions that were made during the prospective risk evaluation?
 - How can prospective and retrospective approaches be used together to help develop measurable REMS goals?
 - How can prospective and retrospective approaches be used together to improve the redesign of existing REMS?
- How would the use of systematic approaches to the evaluation of risks impact the process for assessing REMS program performance?