ENGELBERG CENTER for Health Care Reform at BROOKINGS

September 25, 2013

Meeting Summary

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

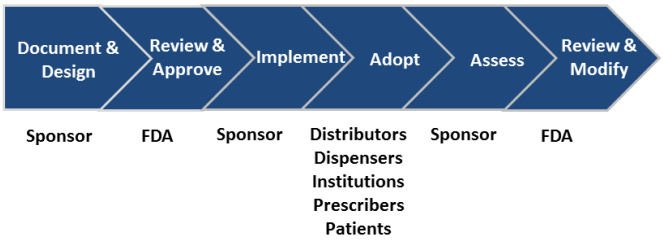
Introduction

In 2007, the Food and Drug Administration Amendments Act (FDAAA) authorized the U.S. Food and Drug Administration (FDA) to require sponsors to develop and implement Risk Evaluation and Mitigation Strategies (REMS), an important component of the FDA's capacity to assure that the benefits of a drug or biologic product outweigh the risks. If appropriately designed, implemented, and assessed, REMS programs have the potential to make valuable and effective drugs accessible to patients while minimizing serious adverse effects. By providing a mechanism for stakeholders to leverage a wide variety of risk management and mitigation tools, including medication guides, communication plans, and elements to assure safe use (ETASU), FDA has been able to use REMS to facilitate access to a host of drugs that may not have otherwise have been approved and allow products to remain on the market with greater confidence.[1] However, the practical application and effectiveness of REMS has been challenged by the lack of standardized approaches, resulting in inconsistency in the design, implementation, and assessment of these programs.

Risk Evaluation and Mitigation Strategies (REMS)

A wide variety of stakeholders are involved in the design, implementation, adoption, and assessment of REMS programs, including industry sponsors (i.e., pharmaceutical manufacturers), regulators, distributors, health care professionals, and patients (see Figure 1).

Figure 1: Development, Implementation, and Assessment of REMS[2]



Designing and Reviewing REMS Programs

Once the potential for a specific drug-related adverse outcome has been identified such that the benefits of the drug may not outweigh the risks, the agency must determine whether, given appropriate

[1] Strom, B. L. (2012) Pharmacoepidemiology, Fifth Edition (eds B. L. Strom, S. E. Kimmel and S. Hennessy), Wiley-Blackwell, Oxford, UK. (p.522).

[2] Slatko, G. "Orientation to Risk Evaluation and Mitigation Strategies (REMS)." Brookings Institution. Washington, D.C. September 25, 2013. Presentation.

labeling, the existing health care system has the expertise, resources, or coordinating capacity to effectively mitigate the risk of a preventable adverse event. If not, then a REMS program may be required. FDAAA gives sponsors the responsibility for designing the REMS' components in consultation with the FDA. Sponsors may be required to submit a proposed REMS as part of a drug application (e.g., new drug application, abbreviated new drug applications, or biologic license applications), or in the post-market setting (e.g., if new safety information becomes available that necessitates regulatory action). Following submission of a REMS program by a sponsor, FDA is responsible for reviewing and, if necessary, recommending modifications to the program.

Implementing and Adopting REMS Programs

Once approved, the sponsor is also responsible for the implementation of the REMS program. Sponsors provide all necessary materials and/or services to the health care providers, distributors, dispensers, and other stakeholders who will adopt the REMS programs within their setting. The sponsor's specific responsibilities vary depending on the REMS components. Those that include communication plans require sponsors to disseminate information to health care providers to encourage implementation and explain certain safety protocols. REMS that include medication guides require sponsors to work with pharmacies, practitioners, or health care settings to ensure that the approved information is dispensed with the drug or biological product.[3] Those that include ETASUs can require product sponsors to develop certification programs for healthcare providers to ensure adequate knowledge of educational materials, risk of drug, and ability to diagnose and treat potential adverse reactions. ETASUs may also require the implementation of patient registries, patient monitoring services (e.g., blood test), and 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.[4]

Assessing and Reviewing REMS Programs

In order to ensure that REMS programs are successfully mitigating the known risk of a drug, product sponsors are required to submit REMS assessments throughout standard intervals of the drug's lifecycle. These assessments are required at 18 months, 3 years, and 7 years after REMS approval, though sponsors may submit additional voluntary assessments or propose modifications to the REMS program at any time.[5] FDA reviews sponsors' proposed assessment plans as part of the REMS approval process. These assessment plans include the information that sponsors are requested to collect in order to determine if the REMS is meeting its goals. Requirements for product sponsors can vary depending on the unique components of each of the REMS program.

Product sponsors also typically develop the methods for assessing their REMS program and submit the completed assessment for FDA review. Following sponsor submission, FDA produces a memorandum which determines whether the REMS program has met its intended goals and/or if modification to the

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[3]Choe, L. "Risk Evaluation and Mitigation Strategies (REMS)." Accessed February 24, 2014. Retrieved from: http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM276838.pdf

[4] Ibid.

[5] 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

program is needed. FDA may request further assessment by the sponsor, if additional information is needed to determine whether a REMS program should be modified.[6]

Challenges in the REMS process

The existing REMS process presents several challenges. First, the FDA review process is confidential, and regulators are limited in their ability to collaborate with external parties beyond the submitting sponsor. Adding to this complexity, REMS programs are generally designed throughout the drug development and review process. As such, the information and knowledge of the drug's risks can evolve rapidly throughout this time, which can present challenges for regulators and sponsors to identify which REMS components will be most effective in mitigating risk. In addition, the further in the review process that the drug's risks are characterized, the less time that sponsors and regulators have to design and review an appropriate mitigation strategy. The ability of sponsors to influence healthcare providers or patients through a REMS program may also be limited, as the FDA does not directly regulate these groups.

More broadly, the lack of consistency and standardization in the development, implementation, and assessment of REMS programs has presented significant challenges for regulated industry, regulators, health care providers, and other stakeholders, creating confusion and making REMS difficult to integrate into existing practices. This lack of consistency is in part an inevitable result of the wide range of risks that are addressed in REMS, but is also brought about because of the variety of stakeholders who participate in REMS development and the continuing evolution in how drug risks are managed since REMS were introduced in 2007.

In addressing these challenges, there are a number of opportunities to gather input from stakeholders involved in risk mitigation to create a more efficient and effective system. Such a system will ideally serve as the foundation to standardize REMS program design by informing industry sponsors in selecting effective REMS tools, supporting systematic evaluation of REMS tools, identifying the root causes of program failures, and developing modifications that could be taken to improve future program effectiveness.

Meeting Objectives

To further explore these issues, the Engelberg Center for Health Care Reform at the Brookings Institution, in cooperation with FDA, held an expert workshop, "Strengthening Risk Evaluation and Mitigation Strategies (REMS) Through Systematic Analysis, Standardized Design, and Evidence-Based Assessment," on September 25, 2013. This workshop served as a forum for a wide array of stakeholders, including FDA, manufacturers, healthcare providers, and key content area experts, to explore strategies for standardizing and strengthening FDA's approach to risk management.

Over the course of the day, participants discussed prospective methods for risk evaluation, implications for standardized approaches in REMS development, the development of a "REMS toolkit" for product sponsors, and enhanced strategies to assess the effectiveness of REMS programs. A summary of the broad objectives, potential opportunities, and challenges associated with REMS standardization is included below.

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[6] 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

Strategies for Identifying and Prioritizing Failures

A proactive, prospective, and systematic approach to risk management may improve both the efficiency of the REMS design process and the effectiveness of REMS programs. A critical aspect of REMS program design is the ability to identify failures that may lead to an increased risk for a drug-related adverse event and prioritizing those failures for appropriate intervention.

Participants emphasized that implementation of a prospective and systematic approach to risk identification can provide a valuable opportunity for discrete analysis of care processes, and allows for systematic discovery and investigation of failures that may not otherwise be identified. Participants noted that this approach may be preferable to current methods for identification and prioritization of risks and failures in the process of outpatient drug use, which may be unstructured and inconsistent, and may result in certain failures or risks being overlooked and unaddressed.

Participants also mentioned that it could be helpful to develop criteria to establish a level of risk, or a threshold that determines when risk mitigation should take place. For example, participants noted it might be helpful to have a specified range of excess incidence of a particular adverse event in which various risk mitigation strategies would be considered. The process for determining the level of risk should be explicit and transparent, and could help specify factors relevant to determining when risk mitigation interventions would be indicated.

Systems used to report and track failures that lead to preventable adverse events and near misses (i.e., a system failure which does not result in an adverse event) can serve as significant sources of information for identifying and prioritizing failures. Participants discussed examples of tracking systems within other industries, such as the Aviation Safety Reporting System (ASRS) in aviation, which collects large amounts of user-reported data for the purpose of identifying system weaknesses and potential future failures. Importantly, the ASRS reporting system allows for anonymous submission, which has encouraged the reporting of failures without a fear of retaliation or negative consequences. This system has led to significant improvements to aviation safety and reliability.

Hospital systems have similarly implemented methods for conducting root cause analysis and reporting preventable adverse events that arise from health care system failures. These systems were implemented to improve patient safety and identify how, when, and why, adverse events occur, with the ultimate goal of preventing them in the future. In patient safety programs within Veterans Affairs (VA) hospitals, preventable adverse events are reported in a non-anonymous, non-punitive system. Participants noted that information gathered from reporting could be analyzed and to better inform REMS design. Mechanisms designed to capture and incorporate information on adverse events and near misses could feed back information into the design process to improve the effectiveness of REMS, and could inform a more complete understanding of the causes, probability and severity of adverse events.

Participants noted a number of relevant theories or frameworks for public health and behavioral interventions could inform the design of REMS programs (e.g., PRECEDE-PROCEED, RE-AIM). These theoretical frameworks are grounded in an existing body of research that could help to inform and predict the effect of an intervention. Such frameworks may also help to establish a threshold for the effect of the intervention.

FMEA as a Potential Model Framework for Identifying and Prioritizing Risks Related to Drugs.

Systematic approaches for failure identification and prioritization, such as Failure Mode and Effects Analysis (FMEA), have been used in various industries for risk mitigation. FMEA is a formal and

systematic approach that examines each basic component of a system for failure, including its hardware, software, personnel, and other functional elements. FMEA is designed to identify when and how a system may fail, assess the relative effects of various failures, and help identify which areas need to be examined to prevent those failures from occurring. Through FMEA, data are analyzed and documented through a step-by-step process which categorizes all potential failure modes, their causes, and determines the relative severity of each (e.g., through assigning Risk Priority Numbers). Analysts can then use this information to plan interventions based on the prioritized list of each failure mode.[7] This type of prospective analysis has been adapted and used in health care delivery settings, through Healthcare Failure Mode and Effects Analysis (HFMEA), for assessment of the medication use process within hospital settings.[8]

Participants noted a number of advantages and limitations in utilizing the FMEA approach. 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.[9] Additionally, it facilitates the consideration of risks that would otherwise have remained undetected. However, the FMEA approach 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 human errors are often the cause of failures within REMS programs.[10]

RxFMEA: An Adaption of FMEA for Drug-Related Risks

At the meeting, participants further explored "RxFMEA," an adaptation of HFMEA developed to identify and mitigate failures related to medication related adverse events. In contrast to FMEA and HFMEA, which are designed for settings where failure processes are more discoverable, RxFMEA has adapted procedures to characterize and mitigate failures in the process of medication use in the "wild state" of outpatient care. Important adaptations include the use of a customized database used to track information about medication use, such as underlying attitudinal or behavioral characteristics that could lead to error or failure, and the use of CIOMS III compatible scoring for adverse events.

Interventions specified by RxFMEA are informed by a variety of human factors and ergonomic insights. Participants observed that while human failure can never be completely eliminated, risk mitigation strategies should aim to reduce the frequency of error and implement back-up systems when failures occur. As a result, RxFMEA is designed to engage two stakeholders in its interventions; one for reduction of error, and one as a back-up to mitigate any failure. When designing such interventions, participants

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[7] 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

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

[9] 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

[10] 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.

also noted that communication of content and learning is not very effective on its own, and that tools or "job-aids", help learners to apply that knowledge.

A number of participants shared their experience utilizing FMEA and RxFMEA while evaluating drug risks and discussing their observations from those experiences. Participants noted that the process is long, resource-intensive, and involves a wide range of stakeholders. Some participants had included ethnographic investigations as part of their RxFMEA processes to learn from stakeholders who have experience in successfully mitigating risks in similar situations. This approach resulted in a wealth of data for analysts, and provided pharmaceutical companies with more confidence in the effectiveness of their interventions.

Many participants agreed that while FMEA is a powerful tool, it requires a large investment of time and resources, and is not suitable for all circumstances. Participants observed that use of FMEA or RxFMEA would require a significant amount of investment and training for pharmaceutical companies, as the relevant expertise and experience is generally not present within most pharmaceutical companies. Due to the resource- and time-intensive nature of FMEA and RxFMEA, participants observed that sponsors and stakeholders may benefit from a structured cost/benefit analysis to limit and prioritize use of the process to only drugs which have safety and risk issues that would benefit from an FMEA analysis.

Additional Considerations for Identifying and Prioritizing Failures

Participants noted that the application of risk mitigation strategies from other industries (e.g., aviation) or narrow healthcare contexts (e.g., hospital systems) could prove difficult to apply within the design and implementation of REMS programs, which must be applied at a national level to address a wide range of risks. Successful approaches must take into account the potential impact on a diverse set of stakeholders, patient populations, and health care settings.

Furthermore, imposing additional requirements on product sponsors during the drug development process may delay product approvals and patient access to medication. While participants noted the potential value of instituting frameworks such as FMEA or RxFMEA within the REMS design and review process, others noted caution in adopting strategies which may be overly burdensome with the potential to result in unintended consequences for patients, providers, or sponsors.

Selecting and Developing Interventions or Tools

Once the risks and system failures have been identified and prioritized, targeted interventions and risk mitigation tools (e.g., medication guides, prescriber training) can be designed and implemented. 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. 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.

Participants noted that different interventions have varying degrees of effectiveness and reliability, and referenced the concept of a hierarchy of controls as a useful heuristic to evaluate the relative effectiveness different interventions. In general, participants noted that risk controls from most effective to least effective are as follows: elimination of the hazard, substitution of the hazard, engineered controls, administrative controls, and education or communication interventions. It was recognized that in many cases elimination, substitution, and engineered controls are not applicable to risks associated with outpatient drug use. However, it was still emphasized that REMS interventions should be designed with the effectiveness of each intervention in mind. Participants observed that as

training and communication is the least effective in mitigating failure, stakeholders should consider potential engineered solutions whenever available.

Human Factors Engineering

Participants discussed how human factors engineering processes can inform REMS design, noting that psychosocial considerations may be critical in developing effective REMS tools. The Communication-Human Information Processing (C-HIP) model and the Interactive Social-Cognitive (ISC) model provide systematic frameworks for understanding how risk information is received, processed, and acted upon. The C-HIP model provides a framework for evaluating the source and channels of risk information and how certain cognitive processes (e.g., attention, comprehension, attitudes, motivation) affect an individual's response to that information. The ISC is an expansion of the C-HIP model which identifies the specific points at which a communication may fail to lead to a desired behavior.[11,12] The ISC model takes into account both situational characteristics such as cost of compliance, social influence, norms, and stress, as well as recipients characteristics such as familiarity, relevance, personality, gender, age, and cognitive ability.[13]

The C-HIP and ISC models may provide a systematic framework not only for designing REMS risk communication tools, but also for identifying and evaluating failures in the communication and comprehension process that can be targeted for improvement.

Checklists

Checklists have proven to be powerful tools for risk management in both aviation and patient safety. Participants observed that the value of checklists is not limited to ensuring that procedures are followed or that critical steps are not missed; checklists also reduce barriers in communication by creating a mechanism to help ensure that various stakeholders are communicating with one another (i.e., through verbal tasks and procedures). Participants discussed the ability of checklists to reduce ambiguity between members of a team, providing important information relating to tasks, responsibilities, expectations, methods, and exceptions.[14] Furthermore, participants stressed checklists' value not only as a compliance tool, but also as a cognitive aid.

Checklists have the potential to reduce failure and improve safety if implemented correctly. Participants noted that checklists are most effective if stakeholders and end users are consulted in their development, and if the checklist is integrated into their standard operating procedure. To this end, checklists can benefit from ethnographic and human factors research. Participants noted that checklists will never be universally applicable, even within a single healthcare setting, as different patients, medications, and co-morbidities could necessitate different checklists.

Additional Considerations for REMS Tool Design and Implementation

Participants emphasized the need to understand the end-users of REMS tools during the design of REMS programs. REMS designers should work collaboratively with end-users (e.g., health care professionals) to identify methods for improvement. In addition, REMS intervention designers need to understand the

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[11] Wogalter, DeJoy, & Laughery (1999). Warnings and Risk Communication. London: Taylor.
[12] Francis; Wogalter, M.S. (2006). Handbook of Warnings. Erlbaum, Mahwah, New Jersey, USA.
[13] Kalsher, M.J., & Williams, K.J. (2006). Behavioral compliance: Theory, methodology, and results. Handbook of Warnings (M.S. Wogalter), Erlbaum, Mahwah, New Jersey, USA. (pp. 313-329).
[14] Gurses, et al. (2008) Systems ambiguity and guideline compliance, *BMJ Quality and Safety*, 17. (pp. 351-359).

characteristics of the target population. Currently, REMS are frequently designed to communicate and mitigate "non-obvious" hazards to the end user. Stakeholders need to define what constitutes a non-obvious hazard, and anticipate the needs of REMS communications recipients. Putting an emphasis on outcomes and potential consequences, such as death and serious adverse events, could help drive adherence to mitigation strategies.

Participants noted that implementation fidelity is critical to success. Failure to implement an intervention or tool as designed could compromise the program's effectiveness. An understanding of the implementation process and the context is important for identifying barriers and developing facilitators of implementation. In the aviation industry, redundancy is employed to ensure that interventions are carried out. Such redundancies can provide additional mechanisms to ensure that REMS tools are appropriately deployed, but it remains unclear what levels would be appropriate for REMS programs. Participants also suggested that issues around access and burden will need to be considered, particularly prior to REMS program implementation.

Balancing Advantages of Standardization with the Need for Tailored Approaches

While participants recognized the potential benefit of standardizing risk identification processes and REMS program designs, many also indicated that the advantages of standardization will need to be balanced with the ability to customize risk mitigation approaches for the unique risks of each drug. REMS design and tool development also needs to take into account the uniqueness of health care delivery settings and individual patient differences.

Participants also emphasized a preference for a balance of standardization and customization, and a process that allows for iterative improvement. It was suggested that the adoption of standards or a standardized framework for REMS design should proceed incrementally, so as to better understand the benefits and burdens of such a systematic approach. Participants also sought to distinguish where standardization efforts might be the most appropriate, and suggested stakeholders focus on inputs to REMS program design, including standards for designing, assessing, and determining the need for a REMS program. In contrast, other participants warned that efforts to standardize REMS tools or interventions could hinder innovation or improvement.

Improving REMS Assessment

REMS assessments play a critical role in determining and improving the effectiveness of each program. Standardization and integration of assessment activities into the REMS design and implementation framework has potential to inform more effective, less burdensome REMS programs. Participants identified a range of challenges, as well as potential strategies to improve the assessment of REMS.

Potential Challenges

Participants identified several challenges that have hindered meaningful assessments of REMS programs. Participants observed that statistical issues have persisted in assessing the effect of REMS programs, including the problem of small or limited sampling frames. Participants also noted the difficulties in systematically and reliably identifying the true effect of REMS programs if a preexisting REMS program or other intervention (e.g., advertising) is already in place at the time of assessment. Additionally, it can be difficult to assess the effectiveness of REMS programs for first in class products, as the product has no pre-REMS safety data for comparison.

Potential Strategies

Participants highlighted existing data sources that may be leveraged to conduct assessments on the effectiveness of REMS programs. These include EHRs and claims data that currently span a range of health care delivery and payer systems. These sources of data can help assess some REMS elements, and can help answer questions about outcomes, exposures, and additional data related to drug safety and use. While the FDA is actively using this data whenever possible, it can be difficult to obtain meaningful data if the population of patients using a REMS drug is small.

An important factor in the effectiveness of REMS assessments is the timing and frequency of the assessments. Participants suggested that REMS programs should be assessed more frequently and earlier in the products lifetime. Such REMS assessments can significantly improve the programs by providing feedback to inform modifications and best practices. Participants emphasized that it is difficult to integrate learning from assessments if they rarely occur or are delayed for too long after implementation. FDA noted that assessments are currently occurring with greater frequency than the law requires.

Participants suggested that the timing of assessments should be tied to patient exposure, and not to a predetermined time point set by regulation or other policy. In addition, scheduled learning cycles for REMS programs would allow for constant development of information that can inform ongoing REMS development and implementation. Such learning cycles could be similar to the three-month quarterly cycles for drug promotion evaluation. In addition, before a product is marketed and a REMS program is implemented, pre-tests or evaluation of a pilot REMS program using an evidenced-based framework may help to improve REMS design and establish a baseline of effectiveness for comparison. While such pre-tests may be valuable, participants noted that it may be difficult to accomplish this while a product is undergoing review.

Participants suggested that certain aspects of REMS assessment should be standardized. Methodologies for assessment and metrics for the success and effectiveness could be standardized and based on established best practices. It may also be helpful to establish a common understanding of how well a REMS program is expected to perform to evaluate the success of a program in meeting its goals. Success could be defined both in terms of processes (i.e., REMS intervention implementation) and outcomes (i.e., effectiveness of a REMS program in reducing failures or changing behavior).

Early Wins

During the meeting, participants outlined practical strategies, or “early wins”, that FDA might explore for broad implementation across REMS programs. A number of these strategies are highlighted below. These strategies represent actionable steps that the agency can take to standardize REMS programs within FDA's well-established review and approval processes. Moving forward, many of the most challenging issues in the standardization and evaluation of REMS will involve areas where multiple stakeholders interact. This includes processes that are beyond FDA's direct regulatory influence, such as the implementation and adoption of REMS by product sponsors and providers. As such, these stakeholders will play an important role in carrying out specific measures and recommendations for further standardization and evaluation.

Participants suggested that stakeholders consider initiating a risk evaluation process during the product design and approval phase of development. While the benefits of risk evaluation may not be immediately apparent during this stage, early assessment may help identify and quantify potential risks

and help to establish risk management priorities. FDA may encourage product sponsors to conduct risk evaluations as part of the standardized REMS design, review, and approval process.

Participants also noted that enhancements to existing mechanisms for labeling and communications can improve or complement REMS programs. Participants observed that in many cases, drug labeling is insufficient, which remains a factor in why REMS interventions may be required. Better integrated electronic systems could provide more effective mechanisms for communication, and systematic analysis could improve characterization and assessment of communication plans. FDA is currently exploring how information about REMS can be better characterized and shared, and how REMS communications can be standardized through use of the Structure Product Labeling (SPL) framework. Participants noted that developing technological solutions can centralize information, tailor messaging for specific patient populations, and coordinate the roles of different stakeholders in delivering information to patients. These solutions could serve to significantly reduce the burdens on stakeholders and improve the effectiveness of REMS programs.

Participants also noted that the nonprescription drug setting might help to inform REMS program design, particularly around health education and risk communication. There are well-established methodologies for evaluation, a significant body of established comprehension research data, and relevant FDA guidances on consumer learning and understanding of drug information and labeling. Participants suggested working towards a standardized vocabulary. FDA has recognized this as an important factor in REMS and has initiated efforts to create a common language to describe REMS variation.