Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)

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EXECUTIVE SUMMARY

Ensuring the safety of drug products—a core component of the FDA mission—is a continuing challenge that demands scientific and organizational rigor across a broad landscape of existing and emerging monitoring and surveillance technologies and tactics. The Food and Drug Administration Amendments Act of 2007 (FDAAA), enacted on September 27, 2007, established FDA's authority to require Risk Evaluation and Mitigation Strategies (REMS) for prescription drug and biological products when it determines that such a strategy is necessary to ensure that the benefits of a drug outweigh the risks.[1] REMS have become a key tool in augmenting FDA's drug safety capacities.

The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted on July 9, 2012, amended FDA's REMS authorities and strengthened the Agency's ability to safeguard and advance public health.[2] Among other things, FDASIA reauthorized the Prescription Drug User Fee Act (known as "PDUFA V," reflecting the fifth reauthorization of PDUFA).

As part of its PDUFA V commitments, FDA agreed, among other things, to measure the effectiveness of REMS, to continue to develop techniques to standardize REMS, to continue to develop techniques to standardize REMS, and with stakeholder input seek to integrate REMS into the existing and evolving health care system.[3] FDA also agreed to hold one or more public meetings with a variety of relevant stakeholders, to include the pharmaceutical industry, federal health care providers, patient groups, and other health care system partners, by the end of FY 2013 to explore greater standardization of REMS where appropriate, with the aim of reducing the implementation burden of REMS for practitioners, patients, and others in various health care settings. In addition, FDA agreed to issue a public report of its findings after analysis of stakeholder feedback (discussed in more detail below), and to identify at least one priority project in each of the following areas, including a work plan for project completion: providing patient benefit-risk information, prescriber education, pharmacy systems, and practice settings.[4]

This report describes stakeholder engagement achieved in FY 2013, and fulfills FDA's PDUFA commitment to issue a report of its findings regarding REMS standardization. It

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[1] Public Law No. 110-85, 121 Stat. 823 (Sept. 27, 2007), available at http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm.

[2] Public Law No. 112-144, 126 Stat. 993 (July 9, 2012); http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/.

[3] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017. http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

[4] Ibid., p. 26. http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

includes suggestions and recommendations received from stakeholders through a variety of methods (public meetings, Advisory Committee meetings, an expert panel workshop, and comments received electronically as well as through teleconferences). Stakeholder feedback guided the Agency in selecting four priority projects within the areas specified by PDUFA V.

Stakeholder Outreach Activities

FDA regularly has sought and received stakeholder feedback with regard to REMS. In July 2010, FDA held a public meeting to obtain input on issues associated with the development and implementation of REMS.[5] 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.[6] Throughout 2013, FDA conducted and/or participated in stakeholder outreach through many mechanisms, including meetings, roundtables, teleconferences, webinars, symposia and seminars.

On July 25-26, 2013, FDA hosted a meeting, "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies," which brought together more than 30 stakeholder organizations and FDA representatives from several offices and divisions within the Center for Drug Evaluation and Research (CDER). This meeting was a key event in FDA's ongoing efforts to hear and learn from stakeholders representing a wide array of organizations impacted by REMS. This meeting explored approaches for designing and measuring the impact of REMS, including evidence-based "best practice" solutions that still retain flexibility in an evolving health care environment.[7]

On September 25, 2013, FDA participated with stakeholders in an expert workshop held at the Brookings Institution, "Strengthening Risk Evaluation and Mitigation Strategies (REMS) Through Systematic Analysis, Standardized Design, and Evidence-Based Assessment." The workshop explored current approaches in the design, development, implementation, and assessment of REMS, limitations of existing methods for the design of REMS programs, and existing approaches to identify, evaluate, and mitigate risks that can inform REMS design. The meeting summary is available online at the Brookings Institution web site.[8]

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[5] For meeting materials, please see http://www.fda.gov/drugs/newsevents/ucm210201.htm.

[6] For meeting materials, please see http://www.fda.gov/Drugs/NewsEvents/ucm292337.htm.

[7] For meeting materials, please see http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm351029.htm.

[8] See http://www.brookings.edu/~/media/events/2013/9/25%20engelberg%20strengthening%20rems/rems_summary_final.pdf.

Stakeholder Feedback

Stakeholder feedback fell into a number of broad areas of opinion and recommendations:

- Many health care stakeholders have successfully implemented REMS requirements.
- Stakeholders are not uniformly impacted by REMS requirements.
- Communication about REMS requirements should be improved.
- There should be flexibility to implement a REMS program based on the nature and variety of health care settings.
- REMS are vital tools that will be increasingly necessary, and content delivery must be streamlined without compromising the content itself.
- FDA should standardize REMS across platforms, media, and delivery technologies and work to fully integrate them into health care systems—which will increase access by both health care providers and patients, and enable improved assessments to further advance standardization.
- FDA should use human factor evaluation approaches like Failure Mode and Effects Analysis (FMEA) to support and standardize REMS program design.
- FDA can improve REMS assessments with a variety of tools and techniques.
- FDA should structure and standardize REMS information.

The four priority projects discussed in detail in this report flow, in part, from these recommendations, and represent the Agency's next steps toward an improved and integrated REMS standardization strategy.

Priority Projects

FDA was directed, as part of the Agency's PDUFA V commitments, to "identify at least one priority project in each of the following areas, including a work plan for project completion: providing benefit/risk information to patients, prescriber education, pharmacy systems and practice settings."[9]

Guided by stakeholder feedback and recommendations, FDA has identified four priority projects, one for each topic area. Each project responds to input the Agency has received regarding significant areas of opportunity for REMS standardization and evaluation efforts. Summaries of each project are below, with more detailed work plans provided in the full report that follows.

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[9] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (p. 26). http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

Project 1
Patient Benefit/Risk Information under REMS: Providing Patient Benefit/Risk Information by Improving Tools for Prescriber-to-Patient Counseling

FDA proposes to:

- Conduct research into existing REMS patient counseling tools, other patient counseling initiatives, and counseling literature to identify the current state of patient counseling regarding medication benefits and risk.
- Seek feedback (e.g., from Advisory Committees, risk communication experts, health care intervention specialists, federal partners, health care providers and others) to identify opportunities to improve upon the content, format, processes, techniques, tools, and delivery of effective counseling within REMS programs.
- Develop a report for stakeholders of findings, counseling processes, and tools that could serve as the basis for designing new tools and validating them in demonstration projects.

Project 2
Prescriber Education under REMS: Prescriber Education—REMS and Continuing Education (CE) for Health Care Providers

FDA proposes to:

- Assess if it is feasible to accredit CE with certain REMS so health care professionals will receive accredited CE when they complete prescriber education activities (such as study and self-assessment tests, modular web-based activities, webinars, etc.). Accrediting bodies will ensure that CE activities developed as part of this project will be in compliance with the CE standards for their organizations. (Accreditation Council of Continuing Medical Education (ACCME), American Nurses Credentialing Center (ANCC), and Accreditation Council for Pharmacy Education (ACPE)).[10]
- For new drugs, determine at what stage the development of CE would best fit in the drug approval process (e.g., pre- or post-approval).
- Evaluate what CE model(s) would be best suited for this type of activity.
- Provide an analysis of time and resources required related to developing and using CE to conduct REMS-related training and/or communication.

Project 3
Pharmacy Systems under REMS: Standardizing REMS Information for Inclusion into Pharmacy Systems Using Structured Product Labeling (SPL)

FDA proposes to:

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[10] Although nurses (other than nurse practitioners) and pharmacists typically do not prescribe, they may be impacted by REMS programs that require training for health professionals other than prescribers.

- Investigate developing SPL for REMS content, including REMS documents, requirements, and materials.
- Develop a structured method to share clear and consistent information about REMS content, including REMS documents, requirements, and materials, with stakeholders and sponsors.
- Make structured, EMS information available to health care providers, patients, and FDA.
- Provide a single source of comprehensive information about REMS programs.
- Facilitate the integration of REMS into pharmacy systems and health information technology, including systems for electronic prescribing.
- Improve the efficiency of review by allowing FDA to receive REMS information from sponsors in a consistent format.
- Support FDA's ongoing standardization efforts by cataloging the similarities and differences between REMS programs.

Project 4
Practice Settings under REMS: Providing a Central Source of REMS Information for Practice Settings

FDA proposes to:

- Investigate a centralized, standardized, user-friendly source of information about what stakeholders are required to do in each REMS program.
- Help stakeholders quickly learn about REMS programs.
- Help stakeholders understand and comply with REMS requirements.
- Allow stakeholders to compare requirements across REMS and minimize confusion associated with complying with multiple REMS programs.

1   INTRODUCTION

Ensuring the safety of drug products—a core component of the FDA mission—is a continuing challenge that demands scientific and organizational rigor across a broad landscape of existing and emerging monitoring and surveillance technologies and tactics. REMS are a key tool in continuing to augment FDA's drug safety oversight capacity. FDAAA, enacted on September 27, 2007, established FDA's authority to require REMS for prescription drug and biological products when it determines that such a strategy is necessary to ensure that the benefits of a drug outweigh the risks.[11]

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[11] Public Law No. 110-85, 121 Stat. 823 (Sept. 27, 2007), available at
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm

FDASIA, enacted on July 9, 2012, amended FDA's REMS authorities and strengthened the Agency's ability to safeguard and advance public health.[12] Among other things, FDASIA reauthorized the Prescription Drug User Fee Act (PDUFA) for the fifth time.

As part of its PDUFA V commitments, FDA agreed to measure the effectiveness of REMS and standardize and better integrate REMS into the health care system, and to continue to develop techniques to standardize REMS and, with stakeholder input, seek to integrate REMS into the existing and evolving health care system.[13] FDA also agreed to, by the end of FY 2013, hold one or more public meetings to include the pharmaceutical industry, other government health care providers, patient groups, and partners from other sectors of the health care delivery system, to explore strategies to standardize REMS, where appropriate, with the goal of reducing the burden of implementing REMS on practitioners, patients, and others in various health care settings. FDA is "to move towards increased integration of REMS into the health care delivery system," and, to that end, "issue a report of its findings by the first quarter of FY 2014 that will identify at least one priority project in each of the following areas, including a work plan for project completion for pharmacy systems, prescriber education, providing benefit-risk information to patients, and practice settings."[14]

This report summarizes stakeholder engagements completed in FY 2013 and fulfills FDA's PDUFA commitment to issue a report of its findings regarding REMS standardization. This report includes suggestions and recommendations received from stakeholders through public meetings, Advisory Committee meetings, an expert panel workshop, comments received electronically (posted to a federal docket), and via teleconferences with stakeholders representing both professional and consumer perspectives. With this stakeholder feedback serving as reference, FDA selected four priority projects within the areas specified by PDUFA V.

This report briefly reviews the background and context for REMS as well as FDA management initiatives for REMS administration and program improvement, summarizes key perspectives expressed by stakeholders, and presents the design and proposed workplans of projects in the four designated priority areas.

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[12] Public Law No. 112-144, 126 Stat. 993 (July 9, 2012);
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/

[13] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (p. 26).
http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

[14] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (p. 26).
http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf

2   OVERVIEW

2.1   Background

The development of REMS evolved from numerous earlier and iterative FDA safety initiatives reaching back to the 1960s. In the mid-2000s, Risk Minimization Action Plans (RiskMAPs) were established to support safe use of products with certain serious risks, and guidance was published that offered sponsors information about how to address product safety concerns using risk management plans.[15] When FDAAA authorized FDA to require REMS for prescription drug and biological products in 2007, many of the principles used to develop RiskMAPs informed the development and implementation of REMS.[16]

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or Act) 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 those applications if the Agency determines that a REMS is necessary to ensure that the benefits of the drug or product outweigh its risks. Section 505-1 also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS if the Agency becomes aware of new post-approval safety information (as defined in section 505-1(b)(3) of the Act), and determines that a REMS is necessary to ensure the benefits of a drug outweighs its risks. In addition, an applicant may voluntarily submit a proposed REMS without having been required to do so by FDA.[17]

A REMS must have a timetable for submission of assessments of the REMS. REMS may include a communication plan for health care providers or require that the applicant develop a Medication Guide or patient package insert.[18] A REMS may also include elements to assure safe use (ETASU), which must include one or more goals to mitigate specific, serious risk(s) listed in the drug or biological product labeling. Depending on the nature of that risk, the ETASU may require one or more of the following: health care

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[15] Guidance for Industry, Development and Use of Risk Minimization Action Plans (the RiskMAP Guidance) (March 2005, pp. 7-12; 18-23),
http://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf

[16] Under FDAAA, products with RiskMAPs that contained elements to assure safe use (ETASU) that were in place prior to the enactment of FDAAA were deemed to have, in effect, a REMS, and sponsors of those products were required to submit a proposed REMS to FDA for approval. The RiskMAP guidance continues to apply to products with RiskMAPS existing at the time of FDAAA enactment but were not deemed to have an approved REMS (i.e., those without ETASU).

[17] See Guidance for industry, Format and Content, Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications (September 2009), p. 2.
http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf

[18] Section 505-1(e) of the FD&C Act, available at http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355-1.htm.

provider training or certification; certification of pharmacies, providers, or health care settings; restricting dispensing to certain health care settings (as in hospitals or infusion centers) or with evidence or other documentation of safe-use conditions (such as liver enzyme tests or pregnancy tests); patient monitoring, and/or that patients using the drug be enrolled in a registry.[19]

Once approved, the REMS document and appended materials serve as the basis for monitoring and enforcement of a sponsor's compliance with REMS requirements.

FDA has approved over 200 REMS since 2007, including six single shared system REMS. Many sponsors have been released from one or more REMS requirements as pertinent safety issues have resolved and FDA has determined that the standard for requiring a REMS is no longer met. As of September 2014, there are 73 approved REMS in place.[20]

Sponsors are required to periodically assess REMS to determine whether the REMS is effectively meeting its intended goal(s) or if the goal(s) or elements should be modified. REMS assessments are to be submitted to FDA at a minimum frequency of 18 months, 3 years, and 7 years after a REMS is initially approved.[21]

2.2   REMS Integration Initiative

To maintain broad oversight of REMS activities within FDA, the REMS Integration Initiative was established. The core objectives of the REMS Integration Initiative include developing guidance on how to apply statutory criteria to determine when a REMS is required, improving standardization and assessment of REMS, and improving integration of REMS into the existing and evolving health care system.[22]

To support the REMS Integration Initiative, the REMS Integration Steering Committee (RISC) oversees the activities of three subordinate work groups with specific deliverables that will fulfill commitments FDA made under PDUFA V.

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[19] Section 505-1(f)(3) of the FD&C Act, available at http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355-1.htm.

[20] For further information, see http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm#information.

[21] See Section 505-1 of the FD&C Act and the Guidance for Industry, Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications (September 2009), p. 5. http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.

[22] For additional information, see http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm350852.htm.

The Policy Work Group is developing a draft guidance about how FDA intends to apply the statutory criteria to determine whether a REMS is necessary to ensure that the benefits of a drug outweigh the risks.

The Design and Standardization Work Group leads FDA efforts to identify best practices to incorporate into future REMS design, as well as appropriate ways to standardize REMS tools and integrate REMS into the health care delivery system. It is issuing this report on priority projects to improve REMS standardization.

The Evaluation Work Group leads FDA efforts to develop an evidence-based approach to assessing the effectiveness and burden of REMS, and is developing a draft guidance on methodologies for assessing the effectiveness of REMS.

Detailed discussion of the ongoing work, objectives, and deliverables of each REMS work group is available online in the *Background Materials for REMS Standardization and Evaluation Public Meeting*.[23]

3   OVERVIEW OF STAKEHOLDER FEEDBACK

3.1   Stakeholder Outreach Activities

FDA regularly has sought and received stakeholder feedback with regard to REMS. In July 2010, FDA held a public meeting to obtain input on issues associated with the development and implementation of REMS.[24] 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.[25] Throughout 2013, FDA conducted and/or participated in stakeholder outreach in a variety of ways, including face-to-face meetings, roundtables, teleconferences, webinars, symposia and seminars, as well as a meeting with the FDA Drug Safety Oversight Board. These activities included a PDUFA stakeholders meeting (March 8, 2013),[26] a roundtable discussion at the American Pharmacists Association Annual Meeting and a Global Alliance of Drug Information Specialists webinar, both in April, and an update and discussion with FDA's federal partners at the Drug Safety Oversight Board meeting on May 16, 2013.[27] On May 23, 2013, FDA participated in a "Trends Emerging in Risk Management" seminar with Lehigh University's Department of

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[23] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm358784.htm#1.2#1.2.

[24] For meeting materials, see http://www.fda.gov/drugs/newsevents/ucm210201.htm.

[25] For meeting materials, see http://www.fda.gov/Drugs/NewsEvents/ucm292337.htm]

[26] For more information regarding the March 2013 meeting, see http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM350913.pdf.

[27] For more information regarding the May 2013 Drug Safety Oversight Board meeting, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm360049.htm.

Industrial and Systems Engineering, "REMS Assessments: An Advanced Concepts Seminar Among Stakeholders."

FDA subsequently hosted a two-day meeting, "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)" on July 25-26, 2013, bringing together over 30 stakeholder organizations and spokespeople with FDA safety experts from several offices and divisions within CDER. This meeting was a key event in FDA's ongoing efforts to hear and learn from stakeholders representing a wide array of organizations impacted by REMS, including pharmaceutical firms, standards development organizations, professional associations, trade organizations (representing retail pharmacies, drug distributors, and pharmacy benefits management firms), communications and medical education vendors, advocacy organizations, and risk mitigation vendors/consultants. Through presentations and discussion, the meeting explored approaches for designing and measuring the impact of REMS, some of which represent evidence-based "best practice" solutions that would still retain flexibility in a rapidly evolving and multifaceted health care environment.[28]

On September 25, 2013, FDA participated with stakeholders in an expert workshop held at the Brookings Institution, "Strengthening Risk Evaluation and Mitigation Strategies (REMS) Through Systematic Analysis, Standardized Design, and Evidence-Based Assessment." The workshop explored current approaches used in the design, development, implementation, and assessment of REMS, challenges and limitations of existing methods for the design of REMS programs, and the development of evidence to inform REMS design. Workshop participants reviewed and discussed existing systematic approaches to identify, evaluate, and mitigate risks that can inform the design of REMS, including the European Medicines Agency's design approach and human factors evaluation methods such as Failure Mode and Effects Analysis (FMEA), Fault Tree Analysis (FTA) and Hazard Analysis and Critical Control Points (HACCP). Participants discussed how these approaches might meet the needs of sponsors, regulators, and other relevant stakeholders. The meeting summary, agenda, and discussion guide are available online at the Brookings Institution Web site.[29]

3.2   Stakeholder Feedback: Opinions and Recommendations

Feedback from stakeholders fell into a number of broad areas of stakeholder opinion and recommendations. The four priority projects discussed in detail at the end of this report stem, in part, from these recommendations, and represent the Agency's next steps toward an improved and more integrated REMS strategy.

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[28] For more information regarding the July 2013 meeting, see
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm351029.htm.

[29] http://www.brookings.edu/events/2013/09/25-engelberg-strengthening-rems.

Key stakeholder opinion and recommendations include:

Health care stakeholders in various settings have successfully implemented REMS.

With approximately six years of experience with REMS programs, many stakeholders, including federal partners both inside the Department of Health and Human Services (HHS) and in the larger federal health care environment (Veterans Health Administration, Department of Defense, Bureau of Prisons), have successfully developed systems to comply with and operationalize REMS. FDA heard that many health care settings have created systems to manage REMS specific to their institutions and also to integrate REMS into their practice settings.

In general, health care settings are more adept with REMS requirements for drugs that are prescribed frequently, as health care providers gain familiarity through routine prescribing in the context of an established in-house (or intra-organization) system or set of processes designed to address one or more REMS, and therefore perceive the REMS burden associated with prescribing these drugs as relatively low.

Stakeholders are not uniformly impacted by REMS requirements.

Across the range of stakeholders who offered feedback, FDA consistently heard that REMS programs affect specific stakeholders and organizational structures differently, presenting a central challenge to standardizing REMS while adequately addressing the differences among multiple stakeholders across an array of health care environments. Numerous variables contribute to the way REMS affect stakeholders, including organization or institution size and mission, different knowledge requirements, perceived burdens of REMS, and the nature and variations of the patient populations being served. Accordingly, the impact of REMS are not equal either among or within stakeholder groups.

FDA was advised that, in many organizations, primary responsibility for knowing the individual REMS requirements for prescribers, patients, and dispensers often falls to the pharmacist. Pharmacists noted they need to clearly understand who (prescribers, pharmacists, nurses, etc.) is accountable for each role or activity under a REMS. FDA heard that pharmacists often monitor individual health care provider responsibilities for REMS with ETASU elements, especially in inpatient health care settings. Some stakeholders expressed concern about the administrative burden that often falls upon the pharmacist to ensure appropriate REMS forms are completed. This seems to be the default in many stakeholder settings, but pharmacist stakeholders note that it can be ineffective, and even undermine the actual purpose of a REMS (i.e., to protect patient safety), when roles and responsibilities are not clearly defined in communications about a REMS.

Among the broader group of health care professionals (physicians, physician assistants, nurse practitioners, pharmacists, nurses), there is relatively wide variation in both levels of understanding of REMS and their perceived burden. These differences also exist

among different medical specialties and practice sites. FDA spoke with internal medicine specialists who currently do not prescribe drugs with REMS, and who noted that simply the existence of a REMS program may deter them from initiating treatment with a drug that has a REMS. In these cases, however, the burden of a REMS is often subjective (i.e., perceived or suspected), or based on anecdotal information, as opposed to being based on direct experience with prescribing a drug with a REMS.

Communication of REMS requirements should be improved.

FDA communications about REMS are often viewed by stakeholders as inadequate, inconsistent, unclear, or simply too difficult (i.e., too time-consuming or too complex) to access, navigate, and digest. This feedback is perhaps the single most frequent concern expressed across the spectrum of stakeholders. Stakeholders communicated that because a variety of REMS elements are employed across different REMs programs, it is important that FDA better communicate the specific activities and obligations each stakeholder must perform as part of each program. This broad and persistent stakeholder concern has implications for virtually all aspects of REMS standardization and evaluation efforts, and is a central consideration for FDA's choice of priority projects, all of which are designed to either directly meet or support a need for improved and more standardized REMS communications.

During stakeholder teleconferences, stakeholders often indicated a lack of understanding or awareness of REMS programs, and commented that FDA should continue to provide general education to stakeholders about REMS programs and the reasons REMS exist. A few stakeholders suggested that REMS be included in course curricula for students in medical, pharmacy, and nursing programs. Other stakeholders suggested a "REMS 101" presentation be included on the FDA REMS Web page to improve general understanding of REMS programs. Several federal partners suggested variations on these themes, such as online training programs and awarding accredited continuing education hours for completing REMS training or educational modules.

Stakeholders often recommended that to gain greater health care provider acceptance of REMS programs, FDA should more clearly outline the reasons that individual products have a REMS. Stakeholders noted that clinicians prescribe many drugs with toxicities, sometimes severe, and many or even most of these drugs do not have REMS. Therefore, FDA should clearly communicate the reasons why some drugs have REMS and others do not, and explain what specific risk is being mitigated through the REMS.

FDA was advised that clearly establishing the reasons for a REMS can also increase a health care provider's sense of ownership and engagement, thus motivating greater participation in a REMS program. Several stakeholders recommended that professional medical associations and societies be invited to communicate with their members regarding REMS, which also may serve to extend the reach of FDA's communications.

FDA also heard that patients must be included in communication and outreach efforts. The Agency was advised that many patients perceive REMS as simply an extra step in an

already complicated and stressful medical care and drug procurement process. Health care providers should be encouraged to help their patients understand REMS not as just another source of "red tape" but as a "living" mechanism designed to enable them to access critically needed drugs that otherwise might not be available, as well as a means of ensuring that patient safety is monitored and protected as rigorously as possible during therapy. Several stakeholders suggested that development of a "REMS for consumers" Web site, using plain language materials, might be useful.

There should be some flexibility to implement a REMS program based on the nature and variety of health care settings.

FDA routinely was reminded about the wide variability between different health care settings in structure and reimbursement systems, particularly in the federal health care system. Administrators from health care settings called for greater flexibility for health care setting enrollment and drug procurement that customizes to (or can be customized to) their settings, whether a small community clinic, small group practice, larger physician group, private or public hospital, networked hospital system, HMO, etc.

REMS are vital tools that will be increasingly necessary, and content delivery must be streamlined without compromising the content itself.

Stakeholders recommended that FDA create, launch, and refine more comprehensive, evidence-based, and organized communications that can meet the needs of integration (function within existing health care systems), clarity and efficiency (providers receive clear, actionable information), and lead to positive clinical outcomes (patients in need receive the drugs they require together with excellent safety monitoring and oversight).

FDA should standardize REMS across platforms, media, and outreach technologies and work to fully integrate them into health care systems—which will increase access by both providers and patients, and facilitate improved assessment to further inform standardization.

A frequently heard stakeholder suggestion is that FDA should work to leverage existing information technology systems to better integrate REMS into standard medical practice and ongoing health care delivery.

FDA should adopt and use a more standardized, systematic approach to REMS design, including using human factors evaluation methods like Failure Mode and Effects Analysis (FMEA).

Several stakeholders are interested in human factors evaluation methods like FMEA or a "Health Care FMEA" that might be deployed to develop criteria for levels of risk (e.g., illness, injury, death) that could prompt regulatory action. One stakeholder recommended using FMEA as a framework for identifying and prioritizing drug-related risks. The stakeholder noted that FMEA might more accurately characterize the process of medication use in "real world" settings and identify ways that care delivery and

medication administration may fail to protect patients from the known or potential risks of drugs. In offering this recommendation, it was noted that while methods like FMEA are powerful tools, they may require a substantial resource investment (time, expense) and may not be practical for use in the development of all REMS programs.

FDA can improve REMS assessments with a variety of tools and techniques.

Stakeholders suggested that REMS assessments might benefit from leveraging of additional data sources (e.g., electronic health records, health claims data) to conduct assessments. A related recommendation is that FDA assess programs earlier and more frequently throughout a product's life cycle, and apply information gleaned from these assessments to modify the REMS if needed. Stakeholders believe the Agency should standardize aspects of the assessment, thereby developing more robust, standardized methodologies that address, for example, the measurement of process and outcomes, as well as whether the REMS changed behavior. They suggested that FDA might consider pilot programs for REMS before full implementation to create a baseline against which the effectiveness of the REMS could be compared.

FDA should structure and standardize REMS information.

Several stakeholders observed that current REMS documentation is not standardized or structured, and generally cannot be easily searched, queried, or managed. Stakeholders suggested use of Structured Product Labeling (SPL) as a possible designated standard that may allow for a centralized, standardized REMS information repository.

4   PRIORITY STANDARDIZATION PROJECTS

As noted in the Introduction to this report, FDA agreed as part of its PDUFA V commitments to measure effectiveness of REMS and standardize and better integrate REMS into the health care system, and with stakeholder input seek to integrate REMS into the existing and evolving health care system. As part of this effort, FDA agreed to identify at least one priority project in each of the following areas, including a project work plan: providing benefit/risk information to patients, prescriber education, pharmacy systems, and practice settings.[30]

The descriptions below cover four priority projects, one for each topic area. Each project was selected with stakeholder feedback in mind, and responds to advice the Agency has received regarding significant areas of opportunity for REMS standardization and evaluation efforts.

While the priority projects described below reflect recurring themes heard from stakeholders, FDA recognizes that stakeholders (notably health care providers and

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[30] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (p. 26). http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

sponsors) need flexibility within any standardized framework to undertake their respective activities in meeting the specific needs of their organizations and/or clinical settings or, for sponsors, product-specific issues.

4.1   PROJECT 1: PATIENT BENEFIT/RISK INFORMATION UNDER REMS

Providing Patient Benefit/Risk Information by Improving Tools for Prescriber-to-Patient Counseling under REMS

4.1.1   Problem Statement

Historically, FDA's primary vehicle for communicating benefit and risk information regarding a product has been through approved labeling that describes a product's indication(s), adverse event profile, and warnings, and that also provides counseling information for patients. In some circumstances, when FDA determines a REMS is necessary to ensure a product's benefits outweigh its risks, FDA may determine that additional patient and/or health care provider communications, training, certification, and/or other restrictions are also required as part of the REMS.

Feedback from stakeholders suggests that when treatment with a drug with a REMS is recommended, patients would value having information to improve their understanding about the product's serious risks, thereby facilitating more informed decisions (made together with their health care providers) regarding whether to initiate or maintain such a therapy. Since patient-directed information should ideally be conveyed to patients in the form of counseling by their health care provider, effective techniques and tools supporting appropriate provider-to-patient counseling about both risks and benefits would be useful.

FDA recognizes that drug products will have a balance of benefits and risks that will be different for individual patient. As such, health care providers will need to determine benefits and risks based on the specific profile and needs of each individual patient, and tailor patient benefit/risk discussions accordingly. This project's deliverable (see *Project Goals and Deliverables* below) will be a report on general improvements to REMS patient counseling tools to enable more comprehensive discussions, but will not proscribe the specific content and/or the extent of benefit information that the health care provider should or should not convey.

4.1.2   Project Overview

FDA proposes to:

- Conduct research into existing REMS patient counseling tools (e.g., patient counseling documents, patient-provider agreements, etc.), other patient counseling initiatives, and counseling literature to identify current tactics and strategies for patient counseling about medication benefits and risk.
- Seek feedback from advisory committees, risk communication experts, health care intervention specialists, federal partners, health care providers and others to identify opportunities to improve upon the content, format, processes, techniques, tools and delivery of effective patient counseling within REMS programs, where

such counseling relates to a drug's serious risks, appropriate use of the drug, and/or a requirements for patients under the REMS program.

- Develop a report of findings and recommended counseling process and tool attributes that could serve as the basis for designing and validating new tools in demonstration projects.
- Develop a standardized counseling tool template that conveys to health care providers key discussion topics, processes, and recommendations for more effectively communicating benefit and risk information to patients, including but not limited to:
  - Informing treatment decision-making made at the time of the initial selection of therapy.
  - Effectively educating patients already receiving treatment about the adverse event risks relative to the benefits they may have observed or experienced, as well as the patient role in recognizing, reporting, and/or mitigating risks that may occur in the future.
  - Supporting patient understanding and retention of key counseling messages by encouraging health care providers to communicate to patients using appropriate language delivered at appropriate intervals, and encouraging physician confirmation of patient understanding.
  - Identifying characteristics of other reliable sources of patient benefit and risk information.

Potential resources and existing tools/initiatives to research will include:

- REMS patient counseling tools and patient-prescriber agreements from various REMS programs.
- Literature on the impact of health care interventions in communicating risks and educating patients (e.g., checklists, disease management, informed consent, etc.).
- Output from workshops and experiences from other organizations on optimizing patient counseling (Institute of Medicine, Centers for Education and Research on Therapeutics, and others).
- Experiences of Advisory Committees and other groups (e.g., Risk Communication Advisory Committee [RCAC], Drug Safety and Risk Management Advisory Committee [DSaRM], Drug Safety Oversight Board) and other subject matter experts.
- Other tools or attributes uncovered during background research.

4.1.3 Project Goals and Deliverables

The purpose of this project is to identify existing counseling practices and tools, as well as opportunities for providing more effective and standardized counseling by health care providers to their patients, in order to improve the effectiveness of communication of serious risks relative to benefits associated with drugs with REMS programs. While FDA recognizes that the purpose of REMS programs is to mitigate risks, stakeholders have communicated to FDA their concern that REMS programs are seen as potentially deterring providers from prescribing, and patients from taking, drugs that may, on

balance, be appropriate for them simply because the product has a REMS. Through this project, FDA hopes to address some of those concerns and assure that patients are receiving appropriate information from their providers regarding products with REMS.

This project will help FDA achieve the following goals:

- Support the standardization of effective health care provider to patient counseling to help improve shared therapeutic decision-making and risk management.
- Encourage health care providers to systematically discuss and educate patients about risks of medications with a REMS, and how those risks should be weighed against the potential benefits of the drug, using initial and follow-up counseling sessions both before prescribing and during treatment.
- Enhance patient involvement, knowledge and understanding of products with REMS.
- Provide a basis for designing and demonstrating the impact of effective counseling instructions, techniques and tools as part of risk mitigation programs.

This project's deliverable will be a report of findings, including a summary of existing tools, feedback from stakeholders and improvements for REMS patient counseling tools.

4.1.4   General Approach

FDA proposes to:

- Research existing REMS tools, counseling initiatives, programs and the literature for evidence of counseling tools, processes, techniques and attributes that support effective education of patients regarding products with REMS;
- Seek information from internal and external stakeholders and experts on effective counseling processes, practices, techniques, tools, attributes and opportunities for improving upon existing REMS counseling tool content, format, techniques, instructions, processes and implementation;
- Seek input to identify sources of reliable medical information for patients to use, and
- Synthesize findings and publish a report.

4.1.5   Project Scope

Defining attributes of tools that enable the implementation of standardized counseling instructions by health care providers to patients will help support safer use of drugs with REMS programs. Such tools will include and complement the patient counseling information contained in the product labeling. It will also support more informed benefit and risk decision making between health care providers and patients when initiating treatment with and using medications that may expose the patient to serious risks.

Although focused on optimization to support effective counseling provided by the prescriber of a medicine to the patient at the start of treatment and intermittently thereafter, these enabling tools and resources also will be relevant to other health care

providers who may be providing counseling or answering patient questions on behalf of the prescriber; to patients seeking to learn more about their medication and whether it is appropriate for them given their underlying condition; individual risk factors and adverse events of concern, and to caregivers supporting patients in identifying and managing adverse event risks.

FDA recognizes there are limitations in the degree to which the Agency will be able to identify, standardize and enable the provision of specific benefit and risk counseling information to patients. For example:

- While general information about important counseling steps and tools can be conveyed to health care providers, unique drug-specific instructions for each individual patient cannot be scripted or proscribed.
- Information about effective counseling methods, techniques, instructions and tools may exist in specific health care practice settings, may be identified during this project, and may influence the recommendations. The ability to objectively distinguish the relative effectiveness of counseling methods/tools without more quantitative assessment instruments and validation methods may be limited.
- FDA will begin with existing tools and initiatives and consult with selected experts, rather than performing a comprehensive *de novo* assessment.
- Patients may vary in their ability to receive, understand, recall, and act upon all of the instructions provided by their health care providers during a single counseling session, particularly if they have just received distressing news about a medical condition. An interactive approach employing adult learning principles and the phased provision of counseling information may need to be considered.
- While it may be feasible to delineate a general set of options for effective counseling tool attributes, topics, methods, and processes, specific recommendations about technologies, reliable Web sites, chat rooms, and expertise may be beyond the scope of this project.

FDA is currently developing various approaches to conducting structured patient benefit/risk assessments, as well as considering the possibility of developing Patient Medication Information (PMI) directly to patients as part of product labeling. While this project may help guide patients to find reliable resources, the goal of this project is to support the communication of risk information to patients indirectly through the counseling they receive from their health care providers about products with REMS programs.

4.2   PROJECT 2: HEALTH CARE PROVIDER EDUCATION UNDER REMS:

REMS and Continuing Education (CE) for Health Care Providers

4.2.1   Problem Statement

During FDA's stakeholder outreach efforts, stakeholders have asked the Agency to facilitate the provision of health care provider CE for the education and training of provided in a REMS program.

Furthermore, assessments of the effectiveness of communication plans (CP) and REMS educational training programs that are not linked to REMS requirements for prescribing or drug distribution demonstrate that stakeholders' knowledge of risks addressed by a REMS, and health care provider levels of participation, have not always met FDA's expectations. Therefore, there is a need to enhance current methods used in REMS to communicate the risks associated with drugs and biological products to health care providers.

REMS-based CE training modules may be effective in improving both stakeholder participation in REMS programs and knowledge of drug-related risks. However, a previous effort to develop and implement a class-wide REMS-based CE training module proved to be a lengthy and intensive process. To include CE training for individual drugs, FDA needs to determine if a more efficient approach would be feasible.

The Agency also must:

- Assess the feasibility of providing CE associated with a specific REMS that is accredited by the Accreditation Council of Continuing Medical Education (ACCME), the American Nurses Credentialing Center (ANCC), and the Accreditation Council for Pharmacy Education (ACPE).[31]
- Determine at what stage in the drug approval process CE development would best fit (e.g., before or after product approval) and what CE model(s) are best suited for this type of activity.
- Provide an analysis of the time and resource requirements associated with developing such CE programs.

Although FDA may want to implement CE along with the health care provider training or communication plan components in REMS, the Agency must consider the following in assessing feasibility and usefulness:

- REMS assessments show that REMS training programs and communication plans are not having the desired effect on prescribers' knowledge of the risks associated with REMS drugs. Assessment reports have indicated low participation rates for non-CE training programs and limited reach for "Dear Health Care Provider" (DHCP) letters, a limitation confirmed by input from stakeholders.

- Health care providers have told FDA that offering REMS training through CE courses would likely attract participants by making it possible for them to obtain needed educational credits.

- Drug sponsors have expressed a desire to offer CE for individual drugs with REMS.

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[31] Although nurses (other than nurse practitioners) and pharmacists generally do not prescribe, they may be impacted by REMS programs that require training for health professionals other than prescribers.

- Changes in communication technology have opened new channels for distributing CE to health care providers, thus potentially increasing reach and participation rates.

4.2.2   Project Overview

- FDA will assess the feasibility of incorporating CE into individual REMS programs that include a communication plan and/or health care provider training components. Individual REMS programs, i.e., REMS that are unique to a specific drug or biological product, are more common; this project is intended to assess the feasibility of developing unique CE programs for single products.

- FDA will define its objectives for REMS CE programs, articulate approaches to achieving them, examine potential barriers to implementing these approaches, and consider ways to address or overcome these barriers. FDA seeks to identify approaches to developing REMS CE that can be implemented, or identify reasons why these approaches are not feasible at present.

- Throughout the process, FDA expects to engage a range of stakeholders, including sponsors, CE accrediting bodies (e.g., ACCME, ANCC, ACPE), CE providers, health care providers, and federal partners.

- At the end of the study, FDA will publish a report of its findings for public comment.

4.2.3   Project Goals and Deliverables

The project goal is to determine the feasibility of developing REMS–related CE training modules for individual products that meet ACCME, ANCC, and ACPE standards, and to develop models for such CE training if possible. The project's deliverable will be a report on the feasibility of REMS-related CE that will include description of potential models for REMS-related CE development and delivery. The report will be published for public comment.

4.2.4   General Approach

FDA will initiate this project by identifying priorities for a REMS-related CE program. These priorities might include, but will not be limited to:

- Use accredited CE courses to educate health care providers about the risks of individual drugs that a REMS addresses and/or obligations and requirements under a REMS.
- Develop REMS CE modules prior to drug approval, without unnecessarily delaying approval.
- Improve participation of health care providers in REMS training.

As priorities are identified, FDA will distinguish between priority objectives of primary importance and those of secondary importance. Those of primary importance include:

- The approach/model should allow health care providers to obtain CE credit for completing REMS training.
- The approach should replace most or all of the training that otherwise would be required of a health care provider in a given REMS.
- The approach should address:
    - Development of REMS training materials;
    - dissemination of training;
    - auditing/approval of training to ensure compliance with REMS requirements, and
    - assessment of training to evaluate effectiveness and make adjustments as needed.

Priority objectives considered to be of secondary importance could include but would not be limited to:

- Allow rapid and efficient CE development.
- Apply CE to as many REMS as possible (e.g., existing, new, pre-approval, post-approval).
- Incorporate best practices in CE and adult learning.
- Limit burden on health care providers.
- Allow for effective monitoring, evaluation, and auditing.

Having identified priority objectives that either are required, or preferred but not required, FDA will then describe approaches for achieving priority objectives.

The Agency also will identify potential barriers to implementation of priority objectives, which could arise in several areas. FDA will investigate whether barriers in each area can be mitigated or overcome by modifying the initial approach.

Areas in which barriers could arise include but are not limited to:

- Potential limitations arising from requirements found in the FD&C Act and its implementing regulations or conflicts with FDA's policies.
- Curriculum development;
- Specification of CE content and messages;
- Financing arrangements;
- Stakeholder cooperation and commitment;
- Accreditation and/or auditing requirements;
- Distribution vehicles; and
- Market acceptance.

FDA will analyze, prioritize and adapt approaches to achieving priority objectives, and eliminate from further consideration approaches whose barriers cannot be mitigated or overcome. FDA will consult with stakeholders to determine their opinions and preferences about Agency decisions regarding priorities and objectives. The Agency will then synthesize findings and publish a report.

4.2.5   Project Scope

This project will address the feasibility of including REMS-related CE as part of the training module for NDAs and BLAs for single products.

The finding(s) may enable FDA to set up a demonstration project for REMS-related CE. However, such a demonstration project will not be part of this project, which will be confined to the assessment of feasibility.

Although findings may be applicable to REMS-related CE that addresses risks shared by drugs in different classes, such as teratogenicity, this type of REMS-related CE will not be addressed in this project.

The scope of this project will include the following three phases:

Phase 1: Define objectives for REMS-related CE

- Obtain input from external stakeholders, including health care providers, on their priorities for CE, including preferred length, mode of delivery, format, etc.
- Review lessons learned from Agency experience with the ER/LA opioid REMS-related CE training program and from REMS assessment data on training programs and communication plans.
- Interview CE industry experts and review CE research literature to determine how REMS-related CE can be made both effective and efficient.
- Define Agency objectives for a REMS-related CE program.

Phase 2: Identify optimum approaches and address barriers to implementation

- Identify possible approaches to developing CE based on information obtained from Phase I.
- Determine whether barriers to approaches can be effectively addressed.
- Modify approaches as needed to address barriers.

Phase 3: Develop Models for REMS-related CE

- Review viable approaches that emerge from Phase 2 against the objectives and priorities identified in Phase 1.
- Identify optimum models for implementation.
- Review models with stakeholders.
- Develop model(s) for REMS-related CE.
- Develop a report of findings for stakeholders.

4.3   PROJECT 3: PHARMACY SYSTEMS UNDER REMS

Standardizing REMS Information for Inclusion into Pharmacy Systems Using Structured Product Labeling (SPL) under REMS

4.3.1   Problem Statement

Stakeholders have expressed concern that REMS materials, tools, strategies, and requirements are inconsistent, even across drugs with similar risks used in similar settings, and are not communicated to stakeholders in a clear and consistent manner. They also told FDA that REMS materials and requirements may be difficult to locate, and specific activities and requirements of various stakeholders (e.g., prescriber, pharmacist, etc.) are not clearly outlined. Furthermore, some stakeholders have difficulty integrating REMS materials and procedures into their existing health information systems and health care delivery processes. Because of these factors, stakeholders reported spending excessive time trying to understand and comply with different sets of REMS requirements and experiencing difficulty ensuring appropriate use of drugs with REMS.

4.3.2   Project Overview

To address the problems described above, FDA, working with standards development organizations (SDOs) if appropriate, will identify an approach for incorporating REMS information into SPL.

SPL is a data standard used to capture and share structured information about drug products. SPL is maintained by Health Level Seven (HL7), an SDO that develops numerous standards for the transmission of information about health care and medical product regulation. The majority of information currently included in SPL, including general product information, the content of drug labeling, and registration and listing information, is entered by a sponsor and submitted to FDA.[32]

SPL is potentially well-suited to addressing the problems of unclear and inconsistent REMS-related information for several reasons:

- **SPL information is easily shared**. When information is placed in SPL format and submitted to FDA, it is automatically uploaded to a central repository maintained by the National Library of Medicine, allowing that information to be shared across the health care system.
- **SPL information is readily incorporated into health information technology**. SPL provides a method for data to be "machine readable," permitting use of the information in health information technology systems such as pharmacy management systems and electronic prescribing.

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[32] More information about SPL can be found at FDA's SPL Resources Web page:
http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

- **SPL incorporates stakeholder input**. The process for incorporating new information into the SPL standard includes established methods for gathering stakeholder input.
- **Industry is familiar with SPL**. Sponsors currently enter information about their drug labels, manufacturing facilities, and products in SPL format, and have many of the requisite tools and knowledge available to capture this information for REMS.
- **FDA also is familiar with SPL**. FDA has tools to accept, review, and support submissions in SPL format, and has significant knowledge of the SPL development process.

4.3.3 Project Goals and Deliverables

This project's purpose is to develop a method to share clear, consistent information about the content of REMS programs, including REMS documents, requirements, and materials. This will help FDA achieve the following goals:

- Make structured REMS information available to health care providers, patients, and FDA.
- Provide a single conduit of comprehensive information about REMS programs.
- Facilitate the integration of REMS into pharmacy systems and health information technology, including systems for electronic prescribing.
- Improve the efficiency of FDA's review of proposed REMS by allowing the Agency to receive REMS submissions in a consistent format.
- Support FDA's ongoing REMS standardization efforts by enabling the cataloging of similarities and differences between REMS programs.

The project's final deliverable will be a revised SPL Implementation Guide that describes how sponsors, health care information system developers, and other stakeholders can share REMS information leveraging the existing SPL standard. This project also may lead to the creation of new SPL data elements and attributes, if needed.

4.3.4 General Approach

In the process of developing this project, FDA has identified key REMS information that may be included in SPL. FDA plans to continue the development of REMS SPL through the following steps:

- Conduct a gap analysis to determine if the capture of key REMS information will require the addition of new SPL data elements and attributes.
- As needed, propose new data elements and/or attributes for HL7 balloting.
- Request SPL terminology for REMS data as necessary. FDA will use existing terminology when possible, but anticipates that certain REMS-specific terminology will be needed to capture structured information about REMS programs.
- Once data elements, attributes, and terminology have been assigned, gather external stakeholder input on these items. If HL7 balloting is required, gather

stakeholder feedback through the HL7 international balloting process. Collect additional feedback through other forums.

- Once balloting is complete and FDA has incorporated relevant stakeholder feedback, update existing SPL Implementation Guide to incorporate new REMS data elements and attributes.
- Update forms and style sheets as needed to accommodate entry and display of REMS SPL information.

4.3.5   Project Scope

FDA proposes using SPL to capture the following REMS information in a structured format:

- General information about REMS such as:
  - which products have REMS;
  - when the REMS was approved and/or modified;
  - which products are part of shared system REMS, and
  - elements included in each REMS.
- The content of the REMS, including:
  - text of the REMS Document, and
  - links to materials appended to the REMS.
- Detailed information about what actions patients, health care providers, and distributors are required to implement in a REMS including:
  - parties that must become certified or enrolled to use the product, and requirements to become certified or enrolled;
  - documentation required by a REMS program to verify the drug was used safely, and
  - restrictions on how REMS product(s) may be prescribed, dispensed, or administered.

The precise information to be shared is subject to change as FDA continues to obtain more feedback on which information is desirable and feasible to incorporate into the SPL standard. Certain information about REMS will remain outside the scope of SPL, including specific details on sponsor implementation of REMS.

4.4   PROJECT 4: PRACTICE SETTINGS UNDER REMS

Providing a Central Source of REMS Information for Practice Settings under REMS

4.4.1   Problem Statement

Many stakeholders rely on FDA's REMS Web page for information about REMS programs. Stakeholders have expressed concern that the Web page does not always have the information they need, and asked that the Web page provide more information about the content of REMS programs, including what is required of specific stakeholders (e.g., whether certain parties need to enroll or become certified as part of the REMS). Stakeholders also asked that currently available information be provided in a more user-

friendly format, and that key information found in the FDA-approved REMS document is summarized to provide a concise overview.

4.4.2   Project Overview

FDA proposes a series of enhancements to its existing REMS Web page. The enhancements would include changes to make the site more user-friendly and to add additional information about individual REMS programs. Where possible, FDA will leverage information captured through SPL (see Project 3, above) to enhance the Web page.

4.4.3   Project Goals and Deliverables

The purpose of this project is to provide a centralized, standardized, reliable, and user-friendly repository of information about REMS, including stakeholders' specific activities and requirements under each REMS program. Doing so will help FDA achieve the following goals:

- Help stakeholders more quickly learn about REMS programs.
- Help stakeholders understand and comply with REMS requirements.
- Minimize the confusion associated with complying with multiple REMS programs.
- Provide stakeholders, researchers, and others with access to convenient, up-to-date and comprehensive REMS information.

4.4.4   General Approach

FDA intends to make a series of enhancements to the Web page, including improvements to the site's functionality and the addition of new information. Some of the specific changes planned for the site are listed in the "Project Scope" section below.
The precise order in which these features will be added has not yet been determined. FDA expects that among the first changes to the Web page will be changes to its layout to help enhance the usability of the page and accommodate future updates. Over time, FDA will add new features and information to the page, iteratively refining the page's layout and content as FDA obtains feedback on its usefulness.

4.4.5   Project Scope

A wide range of stakeholders use the REMS Web page, including health care providers, patients, researchers, and health information technology vendors. These stakeholders vary in the information they need, the format in which they prefer to receive information, and their overall level of knowledge about REMS. Therefore, changes planned for the Web page will be broad in scope, providing stakeholders with a wide range of REMS information and various modes of access to that information.

FDA's Web page already provides general information about REMS programs, such as:

- Which products have REMS;

- when each REMS was approved and/or modified;
- which products are part of a single shared system REMS, and
- elements included in each REMS.

To ensure information is accessible to a wide range of stakeholders, FDA intends to make a series of changes to the Web page, including:

- Create a simpler and more user-friendly page, with key information about REMS programs available at a glance.
- Provide answers to frequently asked questions (FAQs) about REMS.
- Provide the ability to identify and locate information about specific REMS programs.
- Provide the regulatory history of REMS programs, ensuring that historical regulatory information is retained on the page even after REMS are modified or released.
- Identify which parties, if any, must become certified or enrolled before prescribing, dispensing or using the product.
- Provide updates when new information is added to the REMS page, including updates on new REMS approvals and modifications.
- Make information on the page available for download in a machine-readable format.

FDA intends to add additional information to the REMS Web page, dependent upon completion of Project 3, which may include:

- requirements that must be met in order to become certified or enrolled;
- whether documentation is required by the REMS program to verify that the drug was used safely;
- what restrictions apply to how products approved with a REMS may be prescribed, dispensed, or administered; and
- links to relevant information, including a product's prescribing information, Medication Guide, and REMS materials.

5   CONCLUSION

With the safety of drug and biological products standing as a core element of the FDA mission, REMS have emerged as an essential tool in augmenting FDA's drug safety capacities.

The priority projects described in this report are designed to address key issues in the implementation and effectiveness of REMS. The selection of these projects, as well as the development of the project work plans, responds to advice FDA received from stakeholders regarding significant areas of opportunity to improve REMS evaluation and standardization. After a variety of outreach activities conducted over several years, including roundtables, focus groups, webinars, and symposia, FDA hosted a major public

meeting in the summer of 2013. At this meeting, more than 30 stakeholder organizations offered a robust array of perspectives and opinion and participated in a vigorous exchange of ideas with numerous CDER experts. Recommendations from stakeholders fell into a number of broad areas, all of which were carefully considered.

FDA remains committed to systematic evaluation and improvement of REMS program implementation, informed by stakeholder feedback and reflecting the dynamic and evolving nature of drug development—and the shared mission of ensuring that patients continue to have access to safe and effective therapies.

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