APhA 2011 REMS white paper: Summary of the REMS stakeholder meeting on improving program design and implementation

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American Pharmacists Association

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**Abstract**

**Objective:** To develop an improved risk evaluation and mitigation strategies (REMS) system for maximizing effective and safe patient medication use while minimizing burden on the health care delivery system.

**Data sources:** 34 stakeholders gathered October 6–7, 2010, in Arlington, VA, for the REMS Stakeholder Meeting, convened by the American Pharmacists Association (APhA). Participants included national health care provider associations, including representatives for physicians, physician assistants, nurses, nurse practitioners, and pharmacists, as well as representatives for patient advocates, drug distributors, community pharmacists (chain and independent), drug manufacturer associations (brand, generic, and biologic organizations), and health information technology, standards, and safety organizations. Staff from the Food and Drug Administration (FDA) Center for Drug Evaluation and Research participated as observers. The meeting built on themes from the APhA’s 2009 REMS white paper.

**Summary:** The current REMS environment presents many challenges for health care providers due to the growing number of REMS programs and the lack of standardization or similarities among various REMS programs. A standardized REMS process that focuses on maximizing patient safety and minimizing impacts on patient access and provider implementation could offset these challenges. A new process that includes effective provider interventions and standardized tools and systems for implementing REMS programs may improve patient care and overcome some of the communication issues providers and patients currently face. Metrics could be put in place to evaluate the effectiveness of REMS elements. By incorporating REMS program components into existing technologies and data infrastructures, achieving REMS implementation that is workflow neutral and minimizes administrative burden may be possible. An appropriate compensation model could ensure providers have adequate resources for patient care and REMS implementation. Overall, stakeholders should continue to work collaboratively with FDA and manufacturers to improve REMS program design and implementation issues.

**Conclusion:** A workable REMS system will require effective patient interventions, standardized elements that limit barriers to implementation for both patients and providers, standardized yet flexible implementation strategies, use of existing technologies in practice settings, increased opportunities for provider input early in REMS design processes, improved communication strategies and awareness of program requirements, and viable provider compensation models needed to offset costs to implement and comply with REMS program requirements.

**Keywords:** Food and Drug Administration, patient care, risk evaluation and mitigation strategies, REMS, pharmacists, health care workers, compensation, standardization, risk management.

At a Glance

Synopsis: The American Pharmacists Association (APhA) convened a group of 34 stakeholders from across the drug delivery spectrum for a 2-day conference to discuss tangible ways to improve and standardize risk evaluation and mitigation strategies (REMS). The Food and Drug Administration (FDA), manufacturers, and other stakeholders want to create a REMS system for maximizing patient safety while minimizing burdens on the health care system. Stakeholders examined clinical interventions deemed most effective in ensuring patient safety and those described as less than optimal. Participants explored models to improve REMS communication and standardize REMS implementation, and they discussed approaches for using existing technology and systems to ensure a workflow-neutral process. Finally, participants discussed options for compensation to ensure a sustainable business model exists for implementing FDA-required REMS programs.

Analysis: The growing number of REMS programs and the lack of standardization required to implement these programs creates a pressing need for health care providers to continue collaborative work with FDA, manufacturers, and other stakeholders to improve the REMS development and implementation process. The increasing administrative burdens imposed by some REMS threaten to limit patient access to these medications. Working with FDA and manufacturers, health care providers and other stakeholders can provide input early in the development and design process to improve REMS programs by identifying effective provider interventions such as personal consultations with patients, developing a standard framework to communicate REMS implementation plans and increase awareness of REMS programs, standardizing implementation tools within that framework to provide consistency across drug classes and provider settings, and implementing a method for compensating REMS-required services to ensure providers have the staff and other resources to assist patients in understanding the risks and benefits of their medications. The resulting REMS framework should be flexible enough to address new risks as they arise with the changing needs of patients and to embrace new technology options as they become available. In addition, an improved REMS system should include a mechanism to capture data on effective and ineffective interventions as well as patient outcomes. Such a system will improve health care delivery, patient safety, and patient access to medications requiring a REMS program.

Proceedings

This white paper discusses the formulation of recommendations for improving REMS programs. The document is organized in the following sections:
- REMS background (page 341)
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- Goals of the stakeholder meeting (page 343)
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- Appendix 2: American Pharmacists Association (APhA) activities related to REMS (page 357)

For purposes of the stakeholder meeting and this document, the terms health care providers and providers are intended to refer to physicians, physician assistants, nurse practitioners, nurses, and pharmacists.

REMS background

In September 2007, Congress enacted the Food and Drug Administration Amendments Act of 2007 (FDAAA; PL 110-85), which expanded FDA’s risk management authority and reinforced the Agency’s authority over the life cycle of a drug product. This law formalized FDA’s role in creating risk management strategies, specified as risk evaluation and mitigation strategies (REMS), and codified a previously informal process between FDA and drug manufacturers to design risk management programs, then called risk minimization action plans (RiskMAPs). FDA now has the authority to require a REMS to ensure that the benefits of the drug outweigh its risks. FDA can require manufacturers to develop and comply with a REMS program as part of a new or abbreviated new drug application, as part of a biologics license application, or after the product has been approved and new safety information is available.

Considering the drug safety continuum, Figure 1 describes where FDA’s authority to require a REMS program for certain medications fits into the drug approval process. REMS programs contribute to the approval process by filling a space that allows a medication to remain on the market or be approved because the REMS program is in place to mitigate certain risks.

Existing REMS framework

The goal of a REMS is to mitigate risks of a drug and help ensure that the benefits outweigh the risks. A REMS may be required to mitigate serious or unexpected serious risks of a drug, thereby providing safe access to a medication that may not otherwise be approved or not remain on the market due to safety concerns. FDA has acknowledged that the implementation of certain REMS are intended to provide safe access for patients to a drug with known serious risks that would otherwise be unavailable.
As outlined in FDAAA, when determining if a REMS is necessary, FDA must consider:

- The estimated size of the population likely to use the drug involved.
- The seriousness of the disease or condition to be treated with the drug.
- The expected benefit of the drug with respect to such disease or condition.
- The expected or actual duration of treatment with the drug.
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- Whether the drug is a new molecular entity.3

FDAAA provides a list of elements that a REMS program may include: a Medication Guide (MedGuide), patient package insert, communication plan, implementation system, and elements to assure safe use (ETASU). A REMS program may use a combination of some or all of these tools. Each REMS is required to have a timetable for submission of assessments. Further defined in the statute, ETASU may include:

- Health care providers who prescribe the drug have particular training or experience or are specially certified.
- Pharmacies, practitioners, or health care settings that dispense the drug are specially trained and/or certified.
- The drug is dispensed to patients only in certain health care settings such as hospitals (e.g., in the manner of a restricted distribution program).
- The drug is dispensed to patients with evidence or other documentation of safe use conditions such as laboratory test results (e.g., using a restricted distribution program through specialty pharmacy, or safe use conditions based on the delivery of direct patient care services and interventions such as medication therapy management [MTM]).

Table 1. Existing REMS framework per FDAAA requirements

<table>
<thead>
<tr>
<th>Required REMS elements</th>
<th>Timetable for assessment of the REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A REMS may include these elements:</td>
<td>Medication Guide</td>
</tr>
<tr>
<td>- Medication Guide</td>
<td>Patient package insert</td>
</tr>
<tr>
<td>- Communication plan for health care providers</td>
<td>Implementation system</td>
</tr>
<tr>
<td>- ETASU</td>
<td></td>
</tr>
<tr>
<td>- Certification and specialized training of prescribers, pharmacies/pharmacists, and other dispensers</td>
<td></td>
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<tr>
<td>- Restricted distribution of a drug to limited settings</td>
<td></td>
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<tr>
<td>- Dispensing to a patient based on evidence or other documentation of safe use conditions, such as lab results</td>
<td></td>
</tr>
<tr>
<td>- Patient monitoring and/or patient registry</td>
<td></td>
</tr>
<tr>
<td>- Prescriber and/or pharmacist registry</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: ETASU, elements to assure safe use; FDAAA, Food and Drug Administration Amendments Act of 2007; REMS, risk evaluation and mitigation strategies.

Source: Reference 1.

Each patient using the drug is subject to certain monitoring.
- Each patient using the drug is enrolled in a national registry.

Table 1 describes the FDAAA REMS framework.

According to the statute, ETASU should not be unduly burdensome on patient access to the drug and should take into consideration patients with serious or life-threatening diseases or conditions; and patients who have difficulty accessing health care (e.g., patients in rural or medically underserved areas). In addition, ETASU should be designed to minimize the burden on the health care delivery system, conform with elements to assure safe use for other drugs with similar, serious risks; and be
Table 2. Number of REMS programs approved by FDA as of March 9, 2011

<table>
<thead>
<tr>
<th>REMS element</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total REMS approved</td>
<td>177</td>
</tr>
<tr>
<td>MedGuide only</td>
<td>123</td>
</tr>
<tr>
<td>More than a MedGuide</td>
<td>54</td>
</tr>
<tr>
<td>Of the 54, those with elements to assure safe use</td>
<td>17</td>
</tr>
<tr>
<td>Of the 54, those with communication plans</td>
<td>37</td>
</tr>
</tbody>
</table>

Abbreviations used: FDA, Food and Drug Administration; MedGuide, Medication Guide; REMS, risk evaluation and mitigation strategies.
Source: Reference 5.

designed to be compatible with established distribution, procurement, and dispensing systems for drugs.4

Manufacturers have 120 days from the time of FDA notification to develop a REMS and submit to FDA for review. Each REMS is required to undergo assessment at 18 months, 3 years, and 7 years, at a minimum. FDA may require more frequent assessments. When a REMS includes an ETASU, that REMS may be accompanied by an implementation plan to monitor the execution of the ETASU by providers, and manufacturers must continuously work to improve the ETASU follow-up by such providers.

FDAAA also permits FDA’s use of the Drug Safety and Risk Management Advisory Committee to gain additional input on the effectiveness and impact of REMS to maximize patient access to safe and effective medications and minimize the burden on the health care delivery system. Finally, FDAAA permits dispute resolution between manufacturers and FDA related to REMS before FDA’s Drug Safety Oversight Board. However, to date, no dispute resolutions have been filed for a required REMS.

For generic drugs (i.e., bioequivalent versions of the innovator drug listed in FDA’s Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations and approved through an abbreviated new drug application), FDAAA has limited the application of REMS to MedGuides, patient package inserts, and ETASU. If there is a communication plan for the innovator, FDA must carry out the plan when a generic is approved. In addition, generics must use a single, shared ETASU system with the innovator product unless a waiver is granted.

Finally, FDAAA provided FDA with the authority to enforce REMS. The statute prohibits a drug from being introduced into interstate commerce if it is in violation of REMS provisions. In addition, FDA may find the drug misbranded under the Food, Drug, and Cosmetic Act, which carries civil penalties for such violations.

REMS statistics
As of March 9, 2011, FDA has approved 177 REMS programs.5 Table 2 provides a breakdown of the elements associated with those programs. These numbers reflect the most recent information from FDA and are in similar proportion to those used at the time of the stakeholders meeting in October 2010. FDA identified 16 products that were deemed to have a REMS because they had a RiskMAP that included ETASU prior to FDAAA.6 FDA’s list of approved REMS is available online at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPa-
tientsandProviders/ucm111350.htm. The vast majority of these REMS were MedGuide-only REMS. FDA expects the number of MedGuide-only REMS to diminish over time due to the draft guidance on MedGuides that FDA published on February 28, 2011, referenced in Appendix 1.

Additional background information on recent FDA and APhA activities related to REMS is available in Appendix 1 and Appendix 2, respectively.

APhA 2010 REMS stakeholder meeting
To engage a broader set of stakeholders on how to formulate sound REMS policy, APhA convened the APhA Risk Evaluation and Mitigation Strategies (REMS) Stakeholder Meeting on October 6–7, 2010, in Arlington, VA. Participants included 34 representatives from:

- National health care provider associations, including representatives for physicians, physician assistants, nurses, nurse practitioners, and pharmacists.
- Patient advocates.
- Drug distributors.
- Community chain pharmacies.
- Drug manufacturer associations, including representatives from brand, generic, and biologic organizations.
- Health information technology, standards, and safety organizations.

In addition, the meeting was observed by staff from FDA’s Center for Drug Evaluation and Research. (See sidebar for a complete list of participants.)

This meeting built on themes from APhA’s 2009 REMS white paper, which identified several strategies to streamline the development and implementation of a REMS system to be feasible and scalable to accommodate the growing number and complexity of REMS.7 (APhA’s 2009 REMS white paper is available at www.japha.org/REMS. See Appendix 2 for additional information about APhA’s REMS activities and ongoing recommendations.)

Goals of the stakeholder meeting
The overall objective of the meeting was to move conceptual discussions of REMS programs to the next level of granularity—toward designing a REMS system that is effective at improving patient safety yet not so burdensome that it limits patient access to medications. Participants discussed actions to improve the current REMS process. The sum of their recommendations focus on ways to increase effectiveness of REMS programs for patient care while limiting the administrative burdens placed on health care providers. An important component of the meeting was discussion of emerging issues related to improving and standardizing the framework of REMS programs. During the meeting, participants focused on five key goals:

- Examining the type of interventions (or tools) that providers have found most effective in ensuring that risks associated with drug products are mitigated under REMS.
- Exploring concrete ideas regarding standardizing REMS and improving communications about REMS programs, including a draft tiered model to communicate risk mitigation activities.
Developing methods by which REMS, regardless of scale, can be implemented using technology and systems that already exist in the provider workspace to ensure that REMS administration will be as “workflow neutral” as possible.

Identifying practice business models that ensure providers are adequately compensated for the time and cost associated with implementing and administering a REMS program.

Determining how best to implement the solutions identified at the meeting.

The following summarizes the robust dialogue from the meeting as participants identified concrete steps toward improving REMS programs. The text is generally organized by the APhA 2010 REMS stakeholder meeting discussion topics. This white paper concludes with a summary list of all recommendations building on the themes from the stakeholder meeting.

Discussion I: Effective provider interventions

For this session, participants considered the role of health care providers in ensuring patient and drug safety. Meeting participants examined the “toolbox” of interventions available to providers to help patients understand the risks and benefits of drug therapy and assessed how effective the interventions are at decreasing identified risks and increasing safe use. Interventions discussed are those referenced in §901 of FDAAA related
to REMS elements (Table 1). Participants also identified and assessed other interventions not mentioned in the statute that providers may use to help patients understand the risks and benefits of medications, such as personal consultation between a pharmacist and the patient. They offered examples of ways to increase the use of effective interventions rather than optimizing less effective ones. The session touched on the need for analytical, qualitative, and quantitative measures to determine an intervention’s effectiveness. Participants also discussed the need for REMS programs to capture outcomes and identify reasons why program components were or were not successful to ensure that programs can be improved based on lessons learned through implementation.

Participants noted that REMS program design should use specific patient interventions that address the specific risk(s) that a REMS program is designed to mitigate. The elements of provider interventions should be flexible and adaptable according to what is or is not effective, and interventions should accommodate the need to evolve and change over time based on the changing needs of the patient. Participants agreed that as REMS programs are developed, the programs must incorporate approaches that maximize effectiveness and access to medications yet minimize burden on patients and providers. It was noted that current intervention strategies are inflexible and difficult to change due to the REMS modification process. Furthermore, adding to the emphasis for standardization of REMS programs, participants discussed the importance of REMS programs being developed with input from front-line providers early in the development process to better design programs that are effective and workable in various practice settings.

As shown in Figure 2, successful REMS activities generally should be aimed at reducing intervention burden while effectively increasing patient safety and outcomes.

**Experiences with effective patient–provider interactions as REMS interventions**

**Personal consultation.** When considering the types of provider interventions available, participants noted that personal consultation, whether in person, by phone, or by e-mail, is one of the most effective provider interventions. Survey data presented to participants by Calign Inc. (G.C. Naphy, National REMS Assessment Project, unpublished data, October 2010) also supported this conclusion. According to the Calign survey, the top interventions that resonate with patients are consultations with a pharmacist and/or physician. It was noted that although nurses, nurse practitioners, and physician assistants were not included in the survey results presented, an important role exists for all providers in interacting with patients and implementing REMS programs in their practice settings in coordination with the patient’s health care team.

Participants suggested that the most effective medication adherence or patient safety programs are generally those that provide personal contact either from a panel of nurses, through pharmacist’s interventions, or by support networks from physicians’ offices. There was general agreement that provider interventions with patients create an opportunity for personal interaction. These interactions include education and reinforcement about the condition and its treatment, the ability to gauge patient understanding, and the opportunity to modify the interaction to the ongoing needs of the patient. There was agreement on the need to better use effective provider interventions as part of REMS elements to mitigate specific risks.

To promote medication safety and to minimize risk(s), participants stressed the value of a set of REMS interventions or tools that are flexible and customized to a patient’s changing needs related to risk mitigation and safe use as their long-term or chronic therapy evolves. Providers could draw on a variety of materials to address patient needs and concerns at the beginning of treatment and at different time points as patients continue through treatment.

**Reduced burden.** Participants noted that the best interventions minimize the administrative and staffing burdens placed on providers and limit burdens on patients while ensuring patient access to medications. For example, they described several cases in which REMS programs encourage and assist patients or providers who need to follow and document REMS requirements. In these cases, electronic systems in prescriber and/or pharmacy operating systems may be in place to deliver reminders to patients or to prompt one-on-one follow-up. These programs also may deliver reminders to providers at critical points in time so that they can help patients comply with program requirements. Such information also could be provided from a REMS administrator database that is “pinged” or accessed electronically through the electronic prescribing or electronic prescription claims adjudication process. In addition, using such electronic systems already existing in workspaces could generate an electronic message back to the provider about REMS requirements and/or elements to complete in order to prescribe or dispense the medication and to maintain compliance with the REMS program.

**Oncology approach.** Participants discussed how oncology’s approach to chemotherapy provides one model for minimizing burden while safely using high-risk/high-benefit medications. Generally, chemotherapy is monitored by physicians, nurses, pharmacists, and other providers who are specially trained to care for patients with cancer. Participants noted that although oncology drugs carry inherent risks, oncology providers plan for these risks to help prevent adverse effects and to ensure adequate staffing is available to provide the needed patient care. Participants noted that the oncology model works well because of its interdisciplinary, team-based approach and shared communications among providers. While serving as a helpful example on how provider interventions are integrated into non-REMS or REMS-required patient care programs, some participants noted that the oncology model may be difficult to replicate in other settings because of the controlled practice environments, integrated network of providers and support staff, and the high motivation of patients. Thus, it may be easier to implement provider interventions as part of a REMS programs in such settings versus nononcology settings. They also cautioned that it may take time for electronic health records (EHRs) and workflow systems used in oncology settings to be compatible or interoperable with those used in nononcology practice settings.
**Patient-centered services and MTM**. Participants discussed how MTM service could be an effective intervention in REMS programs to better ensure the safe use of medications by addressing specific risk(s) that a REMS program is designed to mitigate. MTM is a distinct service or group of services that optimize therapeutic outcomes for individual patients.8 As part of a model framework for MTM services and personal interactions with the patient, pharmacists assess and evaluate a patient’s complete medication therapy regimen and then work with the patient and others on the health care team to focus on effective medication use and patient safety.9 The interaction between pharmacist and patient provides a unique opportunity to educate, identify problems, monitor drug therapy effectiveness, and follow-up with other health professionals. Participants thought that REMS programs should incorporate aspects of MTM services because REMS-required components, such as providing patient education about the benefits, risks, and appropriate use of a medication, are part of the MTM framework and are effective.

Participants suggested that patient-centered services such as MTM could be useful in integrated care models for REMS implementation because of the patient–provider interaction and emphasis on patient safety. Participants discussed how REMS programs could be designed with MTM as the ETASU specific to dispensing based on safe use conditions. Participants suggested that REMS programs should incorporate aspects of MTM services because REMS-required components, such as providing patient education about the benefits, risks, and appropriate use of a medication, are part of the MTM framework and are effective.

Participants described patient safety issues surrounding REMS that are part of the much larger challenge in health care delivery. Management of increasingly complex medications may require more than a REMS program. They suggested that health policy must address drug risk and focus on effective ways to manage those risks across all sectors of the health care system. Integrated patient care models and services that use MTM could improve oversight of drug delivery and positive patient medication-related outcomes.

**Optimizing REMS-required elements**

In addition to discussing effective options for patient–provider interactions as REMS interventions, participants explored other currently used REMS elements that may be suboptimal from ei-
ther a provider or patient perspective. Participants noted that a number of resources required by existing REMS used to convey risks and benefits to patients could be improved to help both providers and patients.

**MedGuides.** There was general agreement that MedGuides, while frequently used as a REMS required element, often are ineffective because of a wide variation in length and detail. Participants noted that patients often describe MedGuides as “risk heavy” with little information on the benefit of a medication, but participants did recognize that MedGuides are written in compliance with current MedGuide regulations. They also learned from the Calign survey that although MedGuides are frequently used, they have decreasing impact on patients over time and may not be a sustainable approach to ensuring safe use. Participants discussed that in the case of patients on long-term or chronic therapy, MedGuides are often reduced to an ineffective yet burdensome exercise for providers to simply comply with the REMS program.

Participants voiced support for FDA’s current initiative to combine MedGuides, consumer medication information, and patient package inserts into one easy-to-read document called patient medication information (PMI). (For additional information on FDA’s PMI efforts, see Appendix 1 and FDA’s PMI public meeting webpage at www.fda.gov/Drugs/NewsEvents/ucm219716.htm.) It was suggested that patient care could be further improved by combining easy-to-understand risk/benefit materials with personal consultations (e.g., MTM) by providers so patients are clear about REMS requirements and safe use of their medication. Discussion also included the need for REMS information and interventions to evolve and be modified to combat patient “fatigue” with repeatedly receiving the same message in the same format. (See Appendix 1 for additional information on FDA’s February 2011 draft guidance to industry on revising the use of MedGuides in REMS programs.)

**Communication plans.** Participants expressed the need to improve communication plans used to relay REMS information to providers. These plans to increase providers’ awareness of REMS and the logistics required to implement a REMS program often involve sending a Dear Healthcare Professional letter or a REMS orientation packet. Participants suggested that the first materials providers receive should include all of the relevant information about REMS program requirements and logistics and should clearly identify who is responsible for implementing each REMS component. Furthermore, participants emphasized that it is especially important for pharmacists to receive all of the information related to REMS implementation requirements for the prescriber, pharmacist, patient, and wholesaler because pharmacists in different practice settings may help coordinate implementation activities and need to know which party is responsible for REMS requirements.

**REMS program design and development.** Participants discussed the importance of working collaboratively with manufacturers and FDA as efforts continue to improve REMS programs. Participants also suggested that manufacturers include input from front-line providers early in the REMS program design and development process. In the past, FDA and manufacturers have agreed to REMS programs that involve an intervention, registration, verification, or other activity by providers that may not have included input from those provider groups prior to approval. When this happens, the programs may have unintended and negative consequences because the developers may be unaware of the impact on the front-line providers responsible for implementing those elements of a REMS. The problem can be exacerbated in cases in which FDA determines that a drug requires a REMS program toward the end of the drug approval process, because manufacturers then must move quickly to develop a REMS program. The tight time frame affords little time to gather feedback from providers on the REMS design and implementation process. By including front-line providers in the early phase of REMS design, details on how the program’s implementation might impact provider setting could be discussed, altered, and improved to increase effectiveness and reduce burdens. In addition, participants noted that such a development and design period could be an opportunity for providers to alert manufacturers about the resources needed to carry out a specific REMS and discuss potential solutions for obtaining those resources.

Participants also suggested that it may be helpful for new REMS programs with ETASU and multiple components to be pilot tested prior to implementation to better ensure that program technical and logistical issues are adequately addressed. Through testing, an assessment could be provided and addressed if the program produces unintended consequences and/or burdens on the health care system.

**Multiple REMS programs.** Participants agreed that the design of REMS programs should be flexible to accommodate different care settings and patient care needs ranging from community pharmacies and hospitals to assisted-living facilities and hospice programs. Unlike some medical practice settings or specialties that may deal with only one type of REMS program, pharmacy practice settings, including community, hospital, and specialty pharmacies, represent unique challenges to providers faced with simultaneously implementing a myriad of different REMS without a flexible framework for uptake and compliance with REMS programs.

**Modifying REMS programs.** When examining the process to modify current REMS programs, participants noted that making minor, nonsubstantive changes to existing REMS programs may take months to implement through the existing modification process. The current modification process requires FDA to review and approve all modifications to an approved REMS before the modifications can be implemented. Participants considered this time lag inefficient and suggested FDA allow manufacturers more options and flexibility to revise REMS programs based on lessons learned through implementation and outcomes measures. Possibly, this process could occur by allowing providers to request waivers from approved REMS protocols to test new program approaches that could then be replicated if successful.

**REMS and workflow.** When participants considered the impact REMS requirements place on provider workflow, they noted that increased staffing is needed to execute REMS programs, particularly given the wide variety and lack of standardization for different programs. Adequate staff is necessary for a number of
activities, including patient consultations, charting or documentation, and claims filing. Participants suggested designing REMS programs to be incorporated into providers’ existing workflows and through using current practice technology infrastructures. (For more on this discussion, see Discussion III on using existing technologies.) They agreed that failing to integrate REMS into existing workflows creates “silo” programs and places unsustainable demands on practice resources. Using existing technologies offers an avenue for improved and seamless implementation of REMS program requirements into provider practices and enables providers to allocate resources appropriately to ensure compliance with the programs.

Participants also suggested a number of options for optimizing REMS programs related to implementation logistics. These included:

- Using a hard stop to ensure that no prescribing and/or dispensing occurs if REMS-required actions have not taken place or if a certain period of time or therapy has elapsed.
- Automating/standardizing patient surveys (and using existing patient information as captured through REMS-required tools to process a prescription).
- Using electronic registries so these systems can become part of the normal provider workflow when required by REMS. (Such registries could be populated with information from the pharmacy management system or EHRs.)

Provider education/training. Participants agreed that when a REMS program requires providers to seek specialized training or education, it may be more efficient to have FDA and manufacturers work with continuing medical education (CME) and continuing pharmacy education (CPE) providers and other appropriate accrediting bodies to develop training materials. FDA could help determine the content based on manufacturer input and safe use factors that could then be used by accredited CME/CPE providers to design courses and make them available to health care providers. In the case of REMS for the long-acting and extended-release opioid medications, FDA has taken steps along these lines.10 (For additional information on the opioid REMS, see Appendix 1.) To encourage provider participation in completing the training, FDA has suggested that sponsors explore appropriate incentives such as CME/CPE credit. Metrics to determine the effectiveness of provider education and/or training also need to be addressed.

At the November 17, 2010, Prescription Drug User Fee Act (PDUFA) V Stakeholders Meeting, FDA included in its draft recommendations for REMS enhancements the need to provide prescriber education through existing CME mechanisms.11 Both accreditation bodies for CME and CPE are consulting with FDA on how to proceed with REMS provider education components.

Session summary

Participants agreed that patient–provider interventions are an important and highly effective tool for risk management in REMS programs. They described several effective approaches to minimize patient risk and offered ways to improve a number of current REMS requirements. Furthermore, they discussed challenges for making REMS requirements workable in various practice settings and the types of resources (e.g., staff, compensation, education) needed to ensure successful implementation. Throughout the discussion, participants returned to the ongoing need for developing standardized REMS tools and for streamlining REMS processes. They noted that a more consistent approach could lessen the burden of implementing REMS and increase efficiency for those who must comply with REMS requirements.

Discussion II: Improving REMS standardization and communication models

Need for standardization

Participants had an engaging dialogue on the need for standardization of REMS programs. FDA has the authority to regulate manufacturers but not health care providers. Nonetheless, REMS decisions made by FDA affect the practice of medicine and pharmacy considerably because prescribers and pharmacists are responsible for implementing FDA-required REMS programs in their practice settings. While both professions support the safe and effective use of medications, the lack of REMS standardization places substantial burdens on medical and pharmacy practices. The administrative and staffing challenges can cause potentially negative impacts on patient access to necessary medications.

Participants discussed provider concerns about REMS with ETASU because these more restrictive elements can be burdensome for providers to implement. Early approved REMS with ETASU lack standardization and continue to vary greatly in the elements required, their implementation, and administrative procedures, though FDA is making efforts to standardize REMS currently under review. Generally, the greater the risk associated with a drug, the more likely ETASU may be necessary.

A host of REMS programs with ETASU exist requiring different procedures and logistics. The challenges posed include but are not limited to separate informed consent forms, enrollment, certification, or attestation, and they are primarily paper based, contributing to further disruption in workflow and patient care in different patient care settings.

For similar medications, an ETASU requirement for one medication may require providers to perform tasks that the ETA-SU for a comparable drug does not require. This lack of uniformity may inadvertently make the drug less available to patients by:

- Encouraging prescribers to prescribe an alternative, less effective drug because no ETASU is included in the REMS for that drug.
- Causing providers to prescribe a different medication that does not require a REMS but may be less therapeutically appropriate.
- Providing considerable disincentive for pharmacies to stock or dispense the product because of burdens.
- Perpetuating confusion regarding REMS elements and administration that leads to suboptimal prescribing, dispensing, or clinical intervention.
- Causing unbalanced communications to patients that overemphasizes risks while undercommunicating the benefit.
- Overwhelming providers who are already dealing with increasing non-REMS burdens, such as insurance demands, prior authorizations, and formulary compliance.
Causing patients to decline necessary therapy because of misplaced concerns, fear, or burdensome REMS requirements.

The lack of standardization for REMS programs may limit provider participation, reduce supply chain efficiencies, reduce patient access, and decrease effectiveness of a REMS program. Contributing factors include the increasing number and the lack of uniformity among REMS with ETASU, the possible competing or conflicting natures of ETASU for similar drugs, and the administrative burdens faced by providers. Participants recognized that as the number of REMS with ETASU continues to increase, so will these problems. Participants advocated standardization as at least a partial solution to this dilemma.

During this session, participants examined improving REMS in two aspects: standardizing REMS elements and organizing REMS into tiers. They explored why standardization is important and which REMS elements might be standardized. The group also discussed the concept of standardized REMS levels first put forth by APhA in the 2009 REMS white paper. Participants were asked to discuss the strengths and weaknesses of a proposed tiered approach of REMS communication while analyzing its functionality.

**Standardizing REMS elements**

Participants agreed that standardization could improve REMS design, implementation, and program outcomes and evaluation. Presently, a wide degree of variability exists among both REMS elements listed in the authorizing statute and the actual implementation tools being used in current REMS programs. Participants suggested that adoption of standard development, implementation, and evaluation processes would give providers a clearer understanding of their responsibilities when prescribing and dispensing REMS drugs, as well as the information they need to share with patients. Participants said it would make sense for FDA to require manufacturers to use standardized REMS elements and provide them with a standard format for developing a REMS program. Without this guidance, participants anticipated moving down a path similar to MedGuides, which vary widely in format and range of information. There also was general agreement that FDA could help providers by publishing guidance on the criteria used to decide whether a REMS is required and how FDA determines the specific tools that a REMS will use.

**Managing similar drug classes or drug risks.** Three concepts emerged in the participants’ discussion of how REMS should work for drugs with similar risks or drugs in the same class.

First, drugs in the same class bearing the same risks should be treated similarly. There was some debate regarding whether a class or group of drugs that shares the same risk should be treated similarly (i.e., if one drug in the class requires a REMS, then all with the same risk profile should require a REMS). Currently, some drugs in certain classes may have a REMS, whereas others do not. If drugs are not treated similarly, participants noted that providers have to keep track of which drugs in the class have REMS and which do not, as well as know the specifics of each individual REMS program. Some participants believed similar treatment could reduce confusion among providers. Participants also noted that when dealing with a class of drugs in which only some drugs have REMS, providers may choose to prescribe drugs in the class not requiring a REMS. They further noted that drug selection influenced by side stepping a REMS could lead to patients receiving less than effective treatment.

On the other hand, a challenge could arise for manufacturers if all drugs in a class are treated similarly. Participants noted that new products may be compared with similar products approved prior to REMS authorization in 2007. They expressed concern that a new drug with a REMS may have to compete with a drug not requiring a REMS and thus may steer prescribing practices to avoid REMS requirements. There was agreement that to address such challenges, it would be helpful if FDA developed and used a set of standards to ensure that drugs with similar sets of risks are given comparable treatment.

Second, participants determined that in some instances, a classwide REMS mandate may not be advisable because some classes contain many products encompassing a wide range of uses and risks. In addition, in a very broad class of drugs like opioids, different drugs and dosage forms may require different safety tools that are not applicable to all drugs in the class. Participants stated that for some classes, imposing a classwide REMS on all drugs in a particular class may be an unnecessary and ineffective burden.

Third, participants concluded that standardization should take into account and accommodate the need for the same REMS intervention for drugs in different drug classes but with the same risk. For example, participants explained that many drugs in different classes have the potential to cause teratogenicity. Regardless of class, appropriate management of this risk requires patient counseling and pregnancy testing for use of all teratogenic drugs. Different drugs that require the same REMS interventions to manage a risk should be categorized similarly and placed in the same grouping with the same requirements regardless of drug class.

**Non-REMS requirements.** Participants suggested that a set of standard tools shared among all health care providers including payers could help streamline steps that providers must follow when working with a REMS drug. Participants described challenging scenarios in which a provider might be required to complete a certain number of REMS elements and then must also carry out additional tasks not explicit in the REMS but required by a payer (i.e., prior authorization). In addition, participants noted that special data elements may be needed to modify existing electronic transaction standards so they can incorporate REMS elements.

**Standard elements.** In general, participants agreed that REMS systems should use existing standards and technology in practice settings. They also discussed the benefit of building REMS compliance requirements into EHR functionality at the point of prescribing. Participants also discussed efforts of standard setting organizations, such as the National Council for Prescription Drug Programs (NCPDP) or other accredited bodies, to develop processes to route REMS queries. Generally,
Proposed tiered REMS model to improve REMS communications
Participants agreed that to implement REMS programs most effectively, providers would benefit from improved and standardized components. More structure and standardization would eliminate much of the confusion that surrounds REMS implementation. Organizing REMS into a tiered approach was suggested in the APhA 2009 REMS white paper. This concept is similar to controlled substances, which are organized into levels known as schedules (i.e., Schedule II through V). Providers have a general idea of the requirements to prescribe and dispense a certain schedule of drug. For example, providers are knowledgeable that Schedule II is the most restrictive level and requires more administrative steps to dispense compared with drugs in Schedules III through V.

To guide the discussion, APhA developed a draft tiered model that could be used to better communicate what is required of providers to implement a REMS program. The goal of the session was to explore what a tiered model might look like and how it might work. Generally, this standard approach would permit providers to know what is expected of them to prescribe and dispense REMS medications, such as required elements and patient interventions, based on the proposed tier. The draft model’s design acknowledges FDA’s authority to determine a drug’s risk and work with manufacturers to approve a REMS program. The tiered approach would be applied only after FDA determined that a REMS was required for a drug and decided which tools would be used in the drug’s REMS program. The draft model, or something similar, could be used in the future to better communicate what is required to implement a REMS program.

Many participants supported the concept of a standardized tiered model to improve communications to providers. They noted that a standard approach could help providers focus on optimal patient outcomes. With a standard communication model in place, providers could more easily accommodate new REMS drugs because they would know which tools would be required and could prepare their practices in advance by allocating resources. Participants also agreed that the format should be flexible to accommodate new needs that might arise. They found the draft communication framework to be a constructive model and thought it could help move forward the discussion of standardization and improve REMS communications.

However, some participants raised concerns for how the proposed model would be used and in determining who was responsible for assigning the tier. Some participants asserted that a communication model should be arranged according to the type of risk posed by a drug rather than the tools used to implement the REMS. Participants mentioned that by focusing on risk, providers may be more likely to follow through on risk mitigation strategies. They suggested that providers who recognize that a particular drug carries a risk, such as birth defects, may be more likely to check to see if the drug has a REMS program and then identify the kind of information they must convey to a patient. The discussion emphasized the need to work with FDA to standardize REMS programs based on the spectrum of risk of a medication.

The APhA draft served as a helpful starting point for further discussion on improving communications about REMS program requirements. Its usefulness at the stakeholder meeting highlights the need for improving overall REMS communications and awareness. Furthermore, the discussion emphasized the need for stakeholders to be a resource for FDA as FDA works to better standardize programs and develop criteria for what triggers a REMS and the specific elements used in a REMS program.

Session summary
Participants agreed that there is a need to improve both standardization of REMS programs and communication strategies about the elements and processes used to implement the programs. Participants also emphasized the need to develop metrics to assess how well REMS programs are achieving their goals of maximizing patient safety and minimizing burden on patients and providers.

Discussion III: Using existing technology in the provider workspace for REMS implementation
As the number of REMS programs continues to increase, providers are faced with increasing burdens on their time to implement the required elements and to be in compliance with the programs. Participants discussed how to use existing or new software platforms and technologies to ensure that prescribing and dispensing a REMS drug is as close to “workflow neutral” as possible. In particular, they examined how existing systems can be used to streamline training for providers, submit successful completion of REMS training or certification, create and maintain patient registries, and verify and maintain REMS database information. The session also identified opportunities for standardization in the electronic formats and infrastructure used in the provider workspace.

Integrating REMS into existing technology systems in practice settings
Participants discussed the critical need to streamline REMS implementation to minimize the time, effort, and cost that provid-
ers expend on REMS administrative activities. In busy practice settings, providers need REMS tools that seamlessly integrate with tools and systems already in use. Using tools and systems created specifically for REMS implementation can create “silos,” isolating REMS activities from regular practice activities and disrupting workflow. Furthermore, participants explained that tools to incorporate REMS activities would need to build in flexibility; as REMS evolve, the tools could be revised based on lessons learned from implementation. There was agreement that it would be helpful for FDA to provide guidance on and require use of standardized processes for implementing REMS provisions so each program implements tools in a similar fashion.

**Using current technology systems.** Participants noted that electronic prescribing platforms, EHRs, and prescription claims adjudication processing currently in place could be used to accommodate REMS requirements. In the case of prescription claims adjudication, participants noted that the technology and NCPDP standards supporting this process could be used to verify REMS-related data requests. Standards could be populated with data fields to transmit prescription data elements to a REMS administrator database that would store REMS-required information for a specific REMS program. Using this system, participants suggested creating a real-time messaging system to alert providers about unfulfilled REMS requirements such as patient registry enrollment or the need for provider education. Participants suggested that burdens could be reduced by establishing patient registries using demographic data created from electronic prescribing systems to create the patient entries for a REMS registry rather than filling out a separate paper form and faxing it to a third party, as is the case for some programs.

Participants suggested that additional data elements could be added as needed to comply with REMS programs. In the case of EHRs, participants noted the importance of ensuring that medications listed in a patient’s EHR link to corresponding FDA drug and/or REMS program information. Such linkages could improve provider access to labeling and safety information as well as REMS program information. Other information contained in EHRs such as patient demographics, progress notes, problems, medications, past medical history, and laboratory data could be accessed by a REMS program administrator for use in REMS programs through Health Insurance Portability and Accountability Act (HIPAA)-compliant transactions. These comments further support the need for integration of standardized EHR systems into pharmacy management systems. (For additional information on interoperability, the electronic exchange of HIT, and a pharmacist/pharmacy provider EHR, go to the Pharmacy e-HIT Collaborative website at www.pharmacye-HIT.org.)

**Unique identifiers.** Participants suggested that a key aspect to creating a workable system is assigning unique identifiers to providers. They suggested that use of the National Provider Identifier (NPI; developed as part of HIPAA and a required field on all Medicare and Medicaid transactions) be the identifier used to track practitioner-specific REMS requirements (e.g., attestation and verification of successful completion of education or certification requirements). Participants also suggested that the NPI could be a key component in developing a REMS tracking system. Participants acknowledged, however, that not all providers—specifically pharmacists—have an NPI because prescription claims processing is built on the pharmacy NPI rather than an individual’s NPI. Participants agreed that by making NPI an integral part of REMS programs, FDA could help to formalize the use of NPI in pharmacy practice and streamline the tracking of provider activity.

Participants expressed concern for tracking REMS requirements and/or verification procedures based on Drug Enforcement Administration (DEA) registration numbers because DEA numbers are not intended for such tracking. REMS cover medications beyond controlled substances, prescribers in hospitals may use the hospital’s DEA facility number instead of an individual DEA number, and DEA registration is not an appropriate route for tracking pharmacists as it is the pharmacy registered with DEA. In addition, participants expressed concern with using DEA numbers in tracking REMS because DEA numbers are not verifiable in real-time transaction and may not accurately reflect recent REMS-related activity (e.g., verification of education) tied to a DEA number. It was noted that if education was tied to a prescribers DEA number, there should not be additional verification procedures beyond the current process used to fill prescription orders for controlled substances.

**Need for improved access to REMS information**

Participants discussed the need to improve awareness of and access to REMS program information. Although information currently may be mailed, communicated electronically, or available through REMS program websites, participants noted the need for a single source of information and resources. They discussed the benefit of FDA’s current website, which lists all approved REMS, but stated that the FDA website would be more useful if it were reformatted to also include specific program implementation materials for each REMS program. Such revisions would improve the functionality of the list of approved REMS and provide additional resources for providers.

A similar concept participants considered was creation of an electronic resource or clearinghouse model that could serve as a source of REMS information and improve access to such information while still protecting patient privacy. A clearinghouse model also could evolve to help providers fulfill such REMS-related tasks as patient enrollment into registries, enrolling and tracking provider education and training, and enrollment verification. In the future, a REMS clearinghouse could be an alternative to using the existing claim transaction process for certain requirements. For providers in practice settings that do not use the prescription claims transaction process, the clearinghouse may offer a more streamlined approach to REMS compliance and implementation. Currently, providers must visit multiple Internet sites to complete these tasks and often are required to supply the same information each time they visit a site. Participants highlighted oncology practice settings efforts to improve access to REMS information and advocating for a clearinghouse-type concept.

Participants said that by capturing provider and patient da-
ta in a single clearinghouse, the tool could be accessed by other providers or groups tasked with implementing REMS programs in various practice settings. This feature also would be useful within a single institution (e.g., in a community pharmacy setting, where a pharmacist may need to verify that a physician has been certified to prescribe a REMS drug). Participants noted that the technologies needed to create the clearinghouse are available and that the user platform of the clearinghouse could be customized depending on the practice setting and needs of the practice. Other suggestions along the lines of a clearinghouse included the possibility of creating a government/industry partnership to oversee a central repository for REMS-related data.

Another potential capability that participants noted regarding an automated REMS system included a link to payers who would be able to determine if REMS requirements were met prior to authorization and reimbursement. By including payers in future electronic REMS systems, REMS requirements could be verified by payers and the system could create a mechanism for payment of services rendered to implement REMS programs and provide REMS medications.

A user-friendly integrated electronic network could make REMS implementation easier to execute, increase awareness and access to information, improve flexibility in implementing programs across various practice settings using different standards and technologies, and more seamlessly incorporate into provider workflows. A more manageable system also could better ensure successful delivery and compliance with REMS programs and thereby improve overall patient safety.

Session summary
Participants agreed that the tools exist to modify current technologies and processes to accommodate REMS into provider workflows and that some form of electronic resource or clearinghouse would help providers navigate REMS requirements. They suggested that a unique identifier be used to track provider activity when needed. In addition, participants recommended that electronic REMS systems account for a variety of settings spanning from community pharmacies to various inpatient and ambulatory settings. Participants agreed that a one-size-fits-all approach will not work; they suggested development of a flexible system affording minimal disruption when moving from one application to another and from one practice setting to another, where different standards and technologies may be used. Participants added that any electronic systems developed for REMS should permit modifications over time as REMS programs evolve. An integrated system also may increase awareness and access to information.

Discussion IV: Ensuring a sustainable business model for REMS-related provider activities
Participants examined the provider’s role in administering REMS and existing compensation models for those activities. They discussed opportunities for expanding the role of providers in administering REMS-required ETASU, including MTM and other patient-centered care models, and explored how those services might be compensated.

Options for reimbursement
Although the REMS statute describes the activities needed to improve patient safety, it does not describe how those activities will be funded. To successfully implement REMS, providers must have sufficient staff, resources, and other capacity. In many situations, particularly in pharmacy, current resources are being fully used and thus any additional activity will require a “net new” addition of resources. Participants noted that complying with REMS programs improves patient safety but in the current environment REMS can be viewed as an “unfunded mandate.” To address possible solutions to funding REMS services, participants discussed the feasibility of seven different options—manufacturers, Medicare, Centers for Medicare & Medicaid Services (CMS) demonstration projects, Medicaid, insurers, legislation, and MTM—that could provide reimbursement to providers.

Participants noted that one of the biggest challenges to building a case for reimbursement is generating data that show the financial impact of REMS services on personnel, equipment, and time. They suggested that well-designed cost analyses could illustrate the recurring costs associated with REMS provider services, including training, patient monitoring, product tracking, and patient surveys. These analyses could be done in all sectors of drug delivery to create an overall picture of the total cost associated with REMS implementation. A quantitative approach also could reveal the value of the investment in REMS. However, participants suggested that while cost–benefit analyses of REMS are needed, a more urgent task is developing a framework to compensate providers for REMS-related services to ensure the resources to implement truly effective REMS programs.

Manufacturers. It was suggested that by working with the federal government, approaches such as fees from manufacturers could be developed and used to compensate providers for real costs on a fair market basis. Potentially, manufacturers could pay for REMS activities related to provider—patient intervention services as well as monitoring and testing services, survey tools, messaging systems within medical and pharmacy practice, similar to those currently funded for claims adjudication, customized medication instructions, and adherence programs. Some of these activities are already sponsored by manufacturers and are part of existing REMS programs. If services are added to the provider practice because of REMS, manufacturers may be able to pay for the service without creating conflict of interest issues. Manufacturers currently pay for some REMS-related services rendered by providers, and that model could be applied to pharmacists and other providers for performance of REMS-required activities. Payments could be paid securely and administered in an auditable manner through a third party to avoid conflicts. Participants from the provider community viewed this as a cost of doing business without which the manufacturers could not keep the drug on the market. However, some participants disagreed, stating that manufacturers should not be required to pay for REMS interventions.

Medicare. Participants discussed how Medicare Part B cur-
rently covers infused products furnished in physician offices and hospital outpatient facilities, and specific to pharmacists, for administering immunizations. Payment covers documentation, the medication itself, and infusing the medication. They noted that while payment mechanisms exist for physicians and hospitals to be compensated for administering a medication (or for pharmacists, administering immunizations), the statute currently does not recognize pharmacists as providers. In addition, the Medicare Part B fee schedules currently do not include REMS-related services.

Participants suggested that an approach with Medicare-related reimbursement may be to create a separate code for REMS activities. Separate codes might include the range of REMS activities related to ETASU. However, participants noted that this option is a challenge for pharmacists because to bill Medicare to reimburse for REMS-related provider services, the Social Security Act would have to be amended by Congress to recognize pharmacists as Medicare providers under Part B and to add clinical pharmacy services to the fee schedule.

For Medicare Part D–covered drugs, an option for payment for services could be similar to the current MTM reimbursement model. However, participants noted several challenges in trying to use Part D as a compensation model. One hurdle is the need to revise the statute to add REMS services not currently included in Part D’s MTM component. Another challenge concerns the restricted patient eligibility criteria for Medicare Part D MTM services. Currently, payment is based on specific targeted criteria for patients such as multiple chronic conditions coupled with multiple drugs and patient spending levels for medications.

Medicaid. Medicaid is another avenue for potential compensation for REMS activities. Each state controls the use of Medicaid funds; therefore, obtaining funds through Medicaid would require a state-by-state effort. Given the current economic situation, states may not be persuaded to allocate funds for REMS-related services and participants further noted that states may be cutting Medicaid funding.

CMS demonstration projects. CMS has authority to undertake demonstration projects to test and measure the effect of potential program changes. CMS could support a demonstration project in which CMS pays for REMS-related services under both Medicare Parts B and D. However, CMS has limited administrative staff and critics may challenge how the project and reimbursement would be funded. Nonetheless, participants discussed the feasibility of pursuing such activities and interest in working with CMS to explore reimbursement options.

Insurers. Participants discussed that public or private insurance companies could pay for REMS services undertaken by providers. Insurance plans would need to build REMS-related activities into their benefit design depending on practice location and services covered. This potential solution may be problematic in that some insurers might agree to pay for identified REMS-related activities while other insurers may chose not to pay for the same services.

Legislation. The REMS statute could be revised to provide payment for REMS interventions. Participants suggested that the PDUFA reauthorization process in 2012 may be an avenue for inserting compensation language into the statute. Participants discussed the need for advocacy groups to consider the most effective compensation models and, if necessary, work with Congress to insert these models into the statute. In addition, altering the current legislation to incorporate payment for services would help ease concerns of manufacturers when they interact with providers. Considering next steps, participants suggested exploring options to work with manufacturers to advocate to Congress and others for creation of a new model for compensating the drug delivery system when complex therapies are involved.

MTM. Participants noted that MTM is one of a handful of programs that focuses on both using drugs safely and helping change patient behavior. MTM also stands out as one of the few ways patient care services provided by pharmacists are compensated. Many of the components that comprise MTM, such as patient counseling, training, and patient surveillance, are billable events. Participants suggested that stakeholders could work with manufacturers and FDA to determine how best to use MTM services in REMS programs and to facilitate payment by manufacturers for pharmacist-provided MTM services related to REMS programs. Participants suggested a tiered payment system for MTM could be considered in which REMS with ETASU or other intensive clinical therapy with monitoring could be compensated at a higher level than other less intense activities.

Presentation of these foregoing compensation options fueled a healthy discussion of the feasibility of seeking reimbursement. On the positive side, participants suggested FDA could communicate with payers to build support for REMS services reimbursement. FDA representatives observing the meeting said that the Agency is interested in learning more about how the costs of REMS programs are absorbed and who might pay for them. Participants noted that this approach may help facilitate higher level discussions within the administration on how to manage costs associated with REMS.

Session summary
To ensure that prescribers and pharmacists have the staff and ability to meet patient care and administrative needs, several compensation models and options were discussed to address participation in REMS programs. Overall, participants suggested that the task of generating compensation was challenging. Each payment option, some argued, would pay different amounts for different services. Participants noted that current state budgets would make compensation from state-run programs unlikely. Altering Medicaid also would be a challenge because the effort would require lobbying each state. In addition, some voiced strongly that manufacturers should pay for REMS activities because they are creating the products requiring REMS. Some participants were concerned that a manufacturer-driven compensation model may present conflict of interest or other issues. However, other participants said it would make sense for manufacturers to help pay for services to ensure their medications are taken safely. Participants also discussed the need for additional information and cost analysis on the overall costs and administration to implement REMS programs.
**Recommendations**

Navigating the regulatory landscape amid the growing complexity of medication therapies requires collaboration between federal agencies, manufacturers, and those involved across the drug delivery spectrum. REMS programs continue to evolve as a tool to mitigate risks associated with medications that otherwise may not be approved or remain on the market. High-risk/high-reward therapies can improve patient outcomes, but they also require close monitoring by providers. Careful management of risks and benefits can create an environment focused on patient care and positive outcomes.

The following general themes and recommendations emerged during the 2010 APhA stakeholder meeting on REMS:

**Standardize design and implementation**

- FDA, manufacturers, and other stakeholders should continue to work together to improve and evaluate the REMS process and limit burden on the health care system.
- Front-line health care providers should be included early in REMS development discussions to better ensure effective and minimally burdensome REMS-related activities are proposed. Provider input can offer practical details on the challenges and effectiveness of REMS programs as they are being designed.
- A REMS program with multiple ETASU components should be tested to ensure technical and logistical issues are addressed prior to launching the REMS program.
- Implementation for REMS programs must include adequate timelines for health care providers and other stakeholders in the health care system to be notified and complete any required education or updates/revisions to operating system in practice settings.
- Stakeholders should contribute to efforts of FDA to standardize REMS programs based on the spectrum of risk of a medication.

**Maximize effectiveness**

- Focus should be given to measuring REMS effectiveness in minimizing patient risk. Metrics are needed to determine which REMS elements are and are not successful and should include the reasons for success or failure. Tangible data can drive replication of good practices and tools, as well as elimination of suboptimal elements.
- REMS programs should have flexibility to evolve as effective REMS elements and patient interventions may change over the course of drug therapy or because of assessment outcomes. REMS elements that are or become ineffective further increase burden and should be revised or removed.

**Optimize interventions**

- REMS interventions must be effective in helping patients use medications safely but should not be overly burdensome to implement or maintain.
- Provider interventions with patients, such as face-to-face or electronic/telehealth consultations, are an effective means of ensuring safe use of medications and should be considered, when appropriate, as a key element of any REMS program. Open dialog between providers and patients is a critical activity to improve patient safety, convey the benefits and risks associated with drug therapies, gauge patient comprehension, and comply with a REMS program.
- When appropriate, MTM services should be incorporated into the prescribing and dispensing process for medications requiring a REMS. MTM as part of a REMS-required ETASU can be an effective patient-specific tool for ensuring safe use conditions and that patient education, understanding, and optimal outcomes are met. Pharmacist MTM services should be used in collaboration with the prescriber activities to provide required interventions.

**Leverage technology solutions**

- Improving the standardization of REMS programs, components, and processes used to implement the programs is essential. Standardization would improve REMS program development and design, implementation, and program outcomes evaluation. REMS programs must be streamlined into existing workflows and not be overly burdensome on the health care system.
- Existing electronic technologies and infrastructures in medical and pharmacy practice settings and standards should be used to improve implementation of REMS programs (e.g., electronic prescribing, EHRs, electronic prescription claims adjudication, NCPDP, and other similar standard platforms).
- Interoperable access to REMS program information should be integrated among providers and practice settings to ensure operational efficiencies in the administration of REMS.
- Technological, educational, and compensatory programs must take into account that helping patients balance medication safety, benefits, and risks is central to creating successful risk mitigation strategies.

**Centralize information**

- A central repository or clearinghouse of all REMS information should be created as a resource to improve provider awareness and access to REMS information. The clearinghouse also should include the capability for providers, using a unique provider identifier, to manage REMS logistics and compliance activities through connectivity with the appropriate REMS administrator database. The clearinghouse would need to provide options for interoperable electronic access through various practice settings and electronic infrastructures and protect patient confidentiality.

**Facilitate communications**

- Improved communications are needed to clearly identify the responsible and accountable parties for implementing different elements of a REMS program; this information should be included in communication plans and letters to health care providers.
- Health care providers need improved and standardized communications about REMS programs and simpler ways to identify the requirements to implement the different programs. A tiered communication model for REMS programs may be an approach to better communicate the require-
ments associated with implementing REMS programs.

Utilize continuing education
- Accredited continuing education (CE) for medical, pharmacy, and other allied health professionals should be used to assist with REMS education and training requirements. Utilization of CE also would serve as incentive to complete REMS-related educational requirements.

Establish adequate resources and compensation
- The amount of documentation, paperwork, and logistics required to implement and comply with REMS-required activities can affect pharmacy and prescriber practices considerably. Practices may need to hire additional staff to implement and complete additional REMS requirements.
- Several compensation models should be explored to address prescriber and pharmacist participation in REMS programs to ensure they have the staff and ability to meet patient care and administrative needs. A viable REMS compensation model must be developed and implemented.

Table 3. Summary of recommendations

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<thead>
<tr>
<th>Standardize design and implementation</th>
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<tbody>
<tr>
<td>Work together (all stakeholders) collaboratively to improve REMS processes and limit burden on the health care system</td>
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<tr>
<td>Standardize REMS programs, components, and processes</td>
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<tr>
<td>Contribute to efforts of FDA to standardize REMS programs based on the spectrum of risk of a medication</td>
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<tr>
<td>Include input from front-line providers early in REMS design and development process</td>
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<tr>
<td>Test logistics of REMS programs with multiple elements prior to implementation</td>
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<tr>
<td>Provide adequate timelines for notification of health care providers and other stakeholders of requirements in new REMS programs</td>
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Maximize effectiveness
- Focus on REMS effectiveness in minimizing patient risk as a primary marker of successful programs
- Encourage flexibility as REMS programs evolve over time in response to outcomes or changing needs
- Engage in continuous improvement of REMS programs, modifying the program to ensure maximum effectiveness in reducing patient risk

Optimize interventions
- Focus on interventions minimizing patient risk while minimizing burden on the health care system
- Consider the utility and benefits of provider interventions as key elements of a REMS program
- Incorporate pharmacist-provided MTM services as a component of a REMS program when appropriate
- Promote open dialogue between providers and patients

Leverage technology solutions
- Leverage existing technology solutions in medical and pharmacy practice settings to improve implementation and operational efficiencies in the administration of REMS programs

Ensure interoperable electronic access to EHR systems with the exchange of relevant data among all providers and practice settings

Centralize information
- Establish a central repository or clearinghouse of all REMS-related information
- Establish mechanism for the electronic exchange of REMS-related information via diverse practice settings and electronic infrastructures while ensuring patient privacy

Facilitate communication
- Identify and clearly communicate REMS program information to providers
- Establish effective communication strategies to health care providers and patients
- Establish standardized strategies to increase REMS awareness and communicate REMS program requirements

Utilize continuing education
- Integrate REMS-related education into professional continuing education programs to facilitate participation and maximize compliance

Establish adequate resources and compensation
- Consider resources required for all stakeholders to implement and comply with REMS programs
- Establish compensation models for individual REMS for prescriber and pharmacist interventions that facilitate participation and minimize burden on practice settings

Overall summary
Due to the increasing number of REMS programs and the lack of standardization among these programs, there is a decisive need for health care providers to work collaboratively with FDA, manufacturers, and other stakeholders to improve REMS development and implementation. All stakeholders would benefit from a more effective and efficient approach to REMS implementation and communication. While health care providers strive to improve patient safety, the growing number and variety of REMS programs make achieving that goal a challenge. In some cases, administrative burdens imposed by REMS may limit patient access to vital medications. Improvements to overcome the challenges currently associated with REMS can be addressed through cooperative efforts.

By working collaboratively, all REMS stakeholders can contribute meaningful input during the early developmental stages to improve REMS programs by (1) identifying effective provider interventions such as personal consultations with patients, (2) developing a standard framework to communicate REMS implementation plans and increase awareness of REMS programs, (3) using existing technologies and standardizing implementation tools to provide consistency across drug classes and provider settings, and (4) implementing a method for compensating REMS-required services to ensure providers have the staff and other resources to assist patients in understanding the risks and benefits of their medications. Ultimately, an improved REMS
framework should be flexible enough to address new risks as they become known. Furthermore, it should have the capacity to embrace new technology options as they become available. The improved system also should include a mechanism to capture data to identify effective and ineffective interventions as well as patient outcomes.

Development and implementation of a dynamic REMS system will facilitate health care delivery, decrease burden on the health care system, increase patient safety, and improve patient access to medications for optimal treatment.

References


Appendix 1. Food and Drug Administration activities related to REMS

To address the challenges associated with risk evaluation and mitigation strategies (REMS) development and implementation, the Food and Drug Administration (FDA) has been meeting with stakeholders to develop new approaches for program design and efficiency. Discussions regarding guidance to industry (i.e., manufacturers) and a proposed classwide opioid REMS have increased the awareness of REMS implementation challenges and the need to address standardization. The following overview provides an update on recent FDA activities related to REMS.

2009 draft guidance to industry


While this document aims to help manufacturers as they develop REMS for submission to FDA, it does not address standardizing REMS to help ensure uniform implementation within and across care settings, among different providers, and across drug products. However, the goal of REMS standardization as it relates to providers is implicit in the statutory text of the Food and Drug Administration Amendments Act of 2007 (FDAAA; PL 110-85, §901, 121 Stat. §931), which requires FDA to ensure that REMS containing elements to assure safe use (ETASU) are not unduly burdensome on patient access.

Stakeholder feedback to FDA

When FDA initially solicited comments on the 2009 draft guidance on REMS, the Agency received feedback from stakeholders reporting that the growth of REMS—both in number and variety—may be placing a significant burden on the health care system. Prescribers and pharmacists advocated that REMS may limit patient access to therapies if providers choose not to participate in a REMS program because it is too burdensome to implement. Providers also raised concerns regarding the additional resources needed and additional costs associated with implementing REMS programs. Moreover, concerns have been raised about the effectiveness of REMS programs and the lack of outcomes research regarding the programs and program components.

Recognizing these concerns and wanting to gather more stakeholder input on REMS requirements, goals, implementation, and effectiveness, FDA reopened the comment period on the draft document and held the 2-day REMS public meeting on July 27–28, 2010. At this meeting, FDA heard from a larger group of stakeholders about strategies to streamline and standardize the REMS process. FDA officials at the meeting noted that as they have gained experience with REMS, they have learned that some of the REMS requirements in FDAAA lack clarity. They also noted that both REMS development and implementation can be challenging. FDA is currently evaluating input from the comment period and stakeholder meetings and considering options for improving REMS programs.
Long-acting opioid REMS
In February 2009, FDA proposed requiring a classwide REMS for long-acting and extended-release opioid medications. FDA held several meetings with manufacturers and stakeholders to gather input on this proposal. In 2010, FDA issued a draft long-acting opioid REMS for consideration. In July 2010, this proposed draft opioid REMS was rejected at a joint meeting of FDA’s Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. On April 19, 2011, FDA announced that it had sent postapproval REMS letters to manufacturers and marketers of long-acting and extended-release opioid medications indicating that a REMS will be required. The goal of the REMS is to reduce risk and ensure access for patients. The REMS will focus on prescriber education, the dispensing of a patient-friendly Medication Guide, and assessment of the program. FDA’s announcement is one step of an overall coordinated intergovernmental effort to address prescription drug abuse being led by the White House Office of National Drug Control Policy. Additional information on the National Prescription Drug Abuse Plan is available at www.whitehousedrugpolicy.gov/prescriptiondrugs/index.html. Additional information on FDA’s opioid REMS, the letter to manufacturers, and other resources is available at www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm.

PDUFA reauthorization activities
Throughout 2010 and 2011, FDA has been in discussions with manufacturers and gathering input from stakeholders on reauthorization of the Prescription Drug User Fee Act (PDUFA), which expires in September 2012. FDA collects PDUFA user fees from manufacturers as one source of funding for drug review activities in combination with Congressional appropriations. In 2007, PDUFA IV was reauthorized through FDAAA, which included REMS authorization. FDA, manufacturers, and stakeholders have recognized that 2012 PDUFA V reauthorization may provide an opportunity to refine and improve aspects of the REMS statute.

At FDA’s November 2010 PDUFA stakeholder meeting, FDA noted that it is engaged in efforts to articulate the criteria required to determine whether a REMS is necessary. The Agency also is looking at the criteria needed to determine which elements of a REMS are required to address the identified safety concerns. In addition, FDA is working to standardize REMS materials and facilitate use of existing pharmacy systems to implement REMS. More information on PDUFA and FDA’s meetings is available on the Agency’s website at www.fda.gov/ForIndustry/UserFees/Prescription-DrugUserFee/default.htm.

FDA draft guidance on MedGuides in REMS
To address the increasing burden of REMS that use only Medication Guides (MedGuides), on February 28, 2011, FDA issued a draft guidance for industry titled “Medication Guides: Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS).” The draft guidance addresses two topics pertaining to MedGuides for drug and biological products:

- Exercising enforcement discretion regarding distribution of MedGuides to patients, their caregivers, and health care providers for administration of a drug to a patient by a health professional or in an inpatient setting.
- Implementing a procedure to establish when a MedGuide can be eliminated or will be required as part of a REMS.

Additional information about the draft guidance is available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.

Improving patient medication information and MedGuides
FDA intends to develop a new patient medication information (PMI) document that services as a user-friendly tool to better ensure patients receive the necessary information to use a drug safely. FDA’s goal is to build on previous efforts to address challenges with duplicative, inconsistent, and difficult-to-understand patient information. PMI would be a new, single, easy-to-read document that combines information currently dispensed to patients through MedGuides, consumer medication information, and patient package inserts. While this initiative is independent of REMS and still in development, future PMI regulations may require revisions to MedGuides used in REMS.

Additional information on PMI and FDA’s September 2010 PMI public hearing is available on the Agency’s website at www.fda.gov/NewsEvents/ucm219716.htm.

FDA non-REMS patient safety activity
Apart from REMS, FDA also has been actively pursuing its Safe Use Initiative. This program, which was unveiled in November 2009, aims to create and facilitate public and private collaborations with the health care community to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing, and evaluating cross-sector interventions with partners who are committed to safe medication use.

For more information on FDA’s Safe Use Initiative: Collaborating to Reduce Preventable Harm From Medications, go online to www.fda.gov/downloads/Drugs/SafetyEvents/ucm187806.htm.

Appendix 2. American Pharmacists Association activities related to REMS
Since the enactment of Food and Drug Administration Amendments Act of 2007 and the subsequent authorization of risk evaluation and mitigation strategies (REMS), the American Pharmacists Association (APhA) has been actively involved in REMS-related discussions. Among these endeavors, APhA has participated in public meetings and workshops sponsored by the Food and Drug Administration (FDA), advisory committee meetings, educational briefings, meetings with manufacturers and the Industry Working Group for opioid manufacturers, and discussions with other REMS stakeholders including pharmacy, pharmacist, medical, nursing, patient, and consumer groups and technology and system vendors.

APhA’s longstanding goals related to REMS are to (1) be a resource for FDA and manufacturers in helping REMS programs to be effective and achieve their intended outcomes without being overly burdensome on the health care system and (2) ensure REMS are implemented to have limited impact (financial and administrative) on the practice of pharmacy. APhA appreciates that FDA has acknowledged the important role of prescribers, pharmacists, and pharmacies in implementing REMS programs and the need to address administrative and workflow challenges.

In addition, APhA has been involved with and supports FDA’s efforts to improve MedGuides and develop a new patient medication information (PMI) document. APhA also supports FDA’s efforts to revise how MedGuides are used in REMS.
APhA 2009 REMS white paper

On July 15, 2009, APhA convened a small panel of stakeholders to explore the development and implementation of standardized solutions to REMS. Meeting participants included representatives of pharmacists, prescribers, researchers, patient advocates, and nurses, and was observed by a representative from FDA. The 2009 meeting explored experiences with existing REMS and discussed options for developing future REMS programs, with an emphasis on a systematic solution that would be feasible for the health care system. Stakeholder meeting participants engaged in open and candid discussion about their experiences and thoughts for moving forward with developing a standardized, system-based process for implementing any REMS program.

As a result of this 2009 meeting, APhA published “White paper on designing a risk evaluation and mitigation strategies (REMS) system to optimize the balance of patient access, medication safety, and impact on the health care system” in the Nov/Dec 2009 JAPhA.6 The APhA 2009 REMS white paper identified several strategies to streamline the development and implementation of a REMS system to be feasible and scalable to accommodate the growing number and complexity of REMS. For a complete list of recommendations from 2009, access the white paper online at www.japha.org/REMS.

APhA REMS messaging

APhA continues to provide input to FDA and other stakeholders on improving REMS programs and implementation. APhA testified at FDA’s 2010 REMS meetings focused on issues and challenges associated with developing and implementing REMS programs, and the need for standardization and use of existing technology infrastructures to better ensure workflow-neutral implementation. At these FDA meetings, APhA and other pharmacy stakeholders have highlighted the role that pharmacists can play in REMS and advocated for use of clinical interventions, such as medication therapy management, as an example of an element to assure safe use and “dispensing to a patient based on evidence or other documentation of safe use conditions.”

APhA’s ongoing recommendations regarding REMS are as follows (reflects public statements and 2009 white paper). A REMS system should demonstrate the following factors:

– Be designed with input from front-line pharmacists and prescribers early in the development process
– Use a standardized, system-based approach that works for any REMS;
– Integrate with existing pharmacy electronic management systems
– Integrate with prescriber medical record and practice management systems, including use of e-prescribing and electronic health records
– Be available to any willing provider
– Not prevent or delay patient access to medication
– Use standardized components and processes to address administrative, logistical and workflow challenges
– Ensure components are proven to be effective in mitigating defined risk(s)
– Ensure components are workable for all stakeholders (patients, prescribers, pharmacists, manufacturers, wholesalers, and system vendors)
– Define stakeholder accountability for implementing specific REMS components
– Clearly define risks to be mitigated and outcomes to be measured through patient monitoring
– Standardize implementation and documentation of patient monitoring provisions
– Standardize implementation and documentation of patient monitoring provisions
– Be designed with achievable and measurable outcomes
– Ensure a feedback loop is designed to allow continuous quality improvement
– Ensure that reasons for failures/successes are documented
– Monitor for unintended consequences that limit patient access, provider participation, or cause shifts in risk to non-REMS drugs
– Provide education to providers on logistics to prescribe and dispense
– Consider education/training for medical and pharmacy continuing education credit (CME and CPE)
– Be pilot tested prior to nationwide launch
– Ensure that components of a REMS serve as an adjunct to, not a replacement of prescriber/pharmacist dialogue with the patient
– Recognize pharmacist-provided MTM as a effective element to assure safe use for a REMS addressing serious risks
– Ensure compensation for patient care services required to implement a REMS program
– Consider the opportunity for REMS to be designed/organized based on levels of intensity or risk to be mitigated (similar to Schedules of controlled substances)

APhA’s REMS-related statements and comments are available on APhA’s website at www.pharmacist.com/GA.