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

American Pharmacists Association

Abstract

Objective: To convene a group of expert stakeholders to develop recommendations for standardizing systems for the implementation of risk evaluation and mitigation strategies (REMS).

Data sources: On July 15, 2009, the American Pharmacists Association convened an expert panel of stakeholders to explore standardized solutions to REMS development and implementation. Meeting participants included pharmacists from various practice settings, physicians, researchers, patient advocates, and a nursing delegate, and the meeting was observed by a U.S. Food and Drug Administration representative. The stakeholders’ recommendations were combined with themes arising from discussion of their experiences with existing REMS, and a review of the literature on REMS and risk management was performed by the author.

Summary: A systematic, standardized REMS process that balances the need to control the risks of medications with the need to minimize the impact on patient access is required. A standardized REMS system could address various aspects of development and implementation, including the creation of specific REMS “levels,” centralized systems for data management and program structure, public education, individualized patient education, provider education, access to medications, pilot testing, outcomes monitoring, and quality of care.

Conclusion: Several strategies to streamline the development and implementation of a REMS system are feasible. Incorporating such strategies is necessary to manage the rapidly growing number of individual and diverse REMS programs that patients and health care providers must navigate. Furthermore, a standardized REMS system could be used to improve quality of care and support patient education and empowerment.

Keywords: Food and Drug Administration, health care administration, health care providers, patient accountability, patient education, pharmacists, provider education, quality of care, REMS, risk evaluation and mitigation strategies, risk management, workflow.

Evolution of risk management programs

Medications have the potential to considerably improve the health and well-being of patients, but medication use is not without risk. The U.S. Food and Drug Administration (FDA) uses several tools, which have evolved over time, to detect, evaluate, prevent, and mitigate adverse events associated with medications as part of the Agency’s mission to protect and promote public health.

A few decades ago, FDA’s drug safety and risk management activities focused primarily on data from a medication’s clinical trials to assess whether identified risks were outweighed by benefits and to determine whether that medication should be approved. However, societal awareness of postmarket medication safety issues has increased and tolerance for adverse events by patients and the public has decreased. In addition, some safety issues do not surface until after a medication has been marketed and used by a broader population. To address these concerns, FDA has increased their efforts to focus on postmarket safety issues associated with medications.

FDA postmarket surveillance seeks to identify problems that were not observed or recognized before drug approval. Tools used for postmarket surveillance include the Adverse Event Reporting System (AERS) and MedWatch. AERS is a database of adverse event reports that supports FDA’s postmarket safety surveillance program for all approved drugs and therapeutic biologics. MedWatch includes a voluntary adverse event reporting program for both health care providers and patients, and it provides communications about risks. These safety announcements include early communications about ongoing safety reviews, public health advisories, and other information for health care professionals. Additional communication activities, such as letters to health care professionals (e.g., Dear Doctor letters) and labeling revisions (e.g., addition of black box warnings) are coordinated with manufacturers.

Despite increasing risk mitigation activities and risk communications from FDA, several medications with known, preventable risks were withdrawn from the market or placed on restricted distribution because of a lack of appropriate patient monitoring or because medications continued to be inappropriately prescribed to patients who had contraindications to the product’s use.

For example, cisapride (Propulsid) was approved in 1993 for treating gastroesophageal reflux disease and was widely prescribed. During the postmarketing period, cisapride was found to be associated with serious cardiac dysrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation when prescribed to patients who had specific known risk factors or were on certain other medications that interact with cisapride. Several risk communication tools were used to prevent the use of cisapride in such patients, including the use of a black box warning, Dear-Health Care Professional letters, an FDA Talk Paper, and information on FDA’s website. (FDA Talk Papers are used to disseminate detailed, accurate information to the media and to guide FDA staff in responding to questions from the public on specific topics of interest.) These efforts did not appear to alter prescribing practices, and cisapride was withdrawn from the general market in 2000. It continues to be available to a small number of patients through a restricted distribution program (i.e., Propulsid Limited Access Program).
Likewise, alosetron (Lotronex) was approved in February 2000 for treating diarrhea-predominant irritable bowel syndrome in women. Within a few months, FDA had received reports of serious adverse events, including death, associated with use of alosetron. As these reports began to emerge, the manufacturer worked with FDA to develop a Medication Guide (MedGuide) to communicate the risks to patients and educate them to prevent serious harm. (MedGuides are FDA-approved patient information leaflets that must be distributed at the point of medication dispensing. They are deemed necessary when FDA determines that patients require certain information to support the safe and/or effective use of the medication.) Professional labeling was revised, and Dear Health Care Practitioner and Dear Pharmacist letters were issued to convey this new safety information.

Despite these communication activities, serious adverse events associated with alosetron use continued to be reported, including three deaths.4 Alosetron was withdrawn from the market in November 2000 and reintroduced in June 2002 under a restricted distribution program that included a MedGuide, a prescriber agreement, and a patient-physician agreement.5 (The use of the term “prescriber” throughout this document means physicians, physician assistants, nurse practitioners, certain pharmacists authorized to prescribe under specified conditions in their state based on collaborative practice agreements, and other health care providers authorized to prescribe prescription medications.)

As these cases illustrate, risk communication alone does not ensure appropriate prescribing practices. These experiences, in conjunction with an increase in the number of medications that have both important benefits and serious risks, led FDA to begin exploring more restrictive risk management programs in the late 1980s. These programs varied in restrictiveness; some required MedGuides for patient education, while other more intensive programs used restricted distribution programs. Examples of more intensive programs include the Clozaril Patient Management System (developed in the 1980s), the thalidomide (Thalomid) STEPS program (System for Thalidomide Education and Prescribing Safety; developed in 1998), and the isotretinoin (Accutane) iPLEDGE program (developed in 2006).

Clozapine (Clozaril), first introduced in the late 1980s for treating schizophrenia, is associated with an increased risk for agranulocytosis, which can be fatal.5 Close monitoring of white blood cell (WBC) counts can identify the development of this adverse event early enough for prompt discontinuation of therapy, resulting in considerable reductions in the morbidity and mortality associated with clozapine use.6 A tightly controlled system of mandatory patient, prescriber, and pharmacist registration that requires adherence to a weekly WBC count was developed to support safe use of clozapine. Under this system, patients receive 1 week’s supply of clozapine at a time and WBC counts must be obtained before each refill (prescribers may write prescriptions that include refills). (The frequency of WBC counts can be reduced if the patient is maintained on clozapine for more than 6 months without a need for treatment interruption or increased monitoring.) In addition, the system allows for a one-time emergency supply of medication without WBC monitoring.

Risk management programs also have been designed to prevent prenatal exposure to a medication. For example, the thalidomide and isotretinoin risk management programs (STEPS and iPLEDGE, respectively) are designed to prevent pregnancy in women using these known teratogens.

Thalidomide was originally marketed outside the United States from 1957 to 1961 as a sedative, tranquilizer, and antiemetic for treating morning sickness.7 It was removed from the market after it was found to cause serious congenital abnormalities. However, before it was removed, approximately 10,000 children were born with thalidomide-related malformations. Shortly after, in 1965, thalidomide was noted to be effective for treating erythema nodosum leprosum (an inflammatory condition that affects patients with leprosy). However, as a result of concerns about teratogenicity, it was not until the late 1990s that thalidomide was introduced in the United States with a strict system intended to prevent prenatal exposure.7 Today, thalidomide is approved in the United States for treating multiple myeloma, erythema nodosum leprosum, and HIV wasting disease. The STEPS program includes restricted distribution; a national registry for prescribers, patients, and pharmacists, central authorization of prescriptions, a patient informed consent form and required phone survey, and required pregnancy testing in female patients of childbearing potential.8

Isotretinoin, which is approved for treating severe recalcitrant nodular acne, is more widely used than thalidomide. The evolution of risk management programs to prevent pregnancy in patients using isotretinoin (including the Pregnancy Prevention Program, the System to Manage Accutane Related Teratogenicity [SMART], and iPLEDGE) provides an example of the use of progressively more restrictive strategies and the impact of these practices on pregnancy rates (Table 1).9,10

When isotretinoin was introduced in 1982, risk management was limited to a warning on the medication’s label. Fetal malformations were reported despite the warning, and as shown in Table 1, progressively more restrictive program elements were added over time.9 On June 29, 2009, the Accutane brand of isotretinoin was withdrawn from the market by the manufacturer, but generic versions remain available.

In recent years, a substantial increase has occurred in the number of medications that have risk management programs. The programs, previously called Risk Minimization Action Plans (RiskMAPs) by a 2005 FDA guidance, varied in restrictiveness; some required restricted distribution programs, while others were limited to MedGuides.11 As of February 2007, 30 products had RiskMAPs.

**REMS: A new approach to managing risk**

Under the RiskMAP system, FDA had the authority to require postmarketing commitments from manufacturers prior to drug approval but could not enforce the commitments after approval. Several concerns were raised that this system did not
provide adequate safety controls and led to calls for greater FDA authority over the postmarketing period.12 On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA; PL 110-85) was signed into law.13 One goal of this law was to improve drug safety by providing FDA with postmarketing authority over drugs and biological products through new risk identification and communication strategies.

FDAAA includes provisions authorizing FDA to require risk evaluation and mitigation strategies (REMS) for medications or medication classes with known serious risks. The law gives FDA the authority to determine whether a REMS is necessary to ensure that the benefits of a drug or biological product outweigh its risks. FDA has the authority to require a REMS as part of the approval process or during the postapproval period if the Agency becomes aware of new safety information about serious risks associated with the use of the medication. FDAAA directs FDA to be very explicit about why a REMS would be necessary to manage the risks of a medication or class of medications.

As defined in FDAAA, a REMS must include a communication plan and may include a MedGuide, patient package insert, and other elements to ensure safe use; may include an implementation system; and generally, innovator and generic sponsors shall use a single, shared system. The components used in a specific REMS can vary. Elements to ensure safe use, which must include goals to mitigate a specific serious risk listed in the labeling of the drug, may include the following requirements13:

- 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 (i.e., through a restricted distribution program).
- The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results.
- Each patient using the drug is subject to certain monitoring.
- Each patient using the drug is enrolled in a registry.
- Physicians who prescribe and/or pharmacists who dispense the drug are enrolled in a registry.

FDAAA directs FDA to be very explicit about why a REMS would be necessary to manage the risks of a medication or class of medications.

Evaluation of the elements of each REMS program is conducted annually by FDA’s Drug Safety and Risk Management Advisory Committee, as required by FDAAA. The committee must seek input from patients, physicians, pharmacists, and other health care professionals about the elements of the program and may issue or modify Agency guidance on how to implement the requirements and modify elements of a drug’s risk management strategy.

### Table 1. Overview of isotretinoin risk management approaches

<table>
<thead>
<tr>
<th>Risk management strategies</th>
<th>Data on pregnancy rates</th>
</tr>
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<tbody>
<tr>
<td>1982 original warning</td>
<td>Manufacturer receives multiple reports of fetal malformations</td>
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<tr>
<td>Warning on label</td>
<td></td>
</tr>
<tr>
<td>1983 revised warning</td>
<td>Reports of fetal malformations continued</td>
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<tr>
<td>Added:</td>
<td></td>
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<tr>
<td>Red label stickers to pharmacies</td>
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<tr>
<td>1988 Pregnancy Prevention Program (PPP)</td>
<td>2.8 to 3.4 pregnancies per 1,000 courses of treatment</td>
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<tr>
<td>Added:</td>
<td></td>
</tr>
<tr>
<td>“Avoid pregnancy” icon and black box warning on package insert</td>
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<tr>
<td>Patient consent form</td>
<td></td>
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<tr>
<td>Package insert noted a requirement for a pregnancy test prior to starting treatment</td>
<td></td>
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<tr>
<td>Package insert stated that two forms of birth control must be used</td>
<td></td>
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<tr>
<td>2001 System to Manage Accutane® Related Teratogenicity (SMART)</td>
<td>2.1 to 2.3 pregnancies per 1,000 courses of treatment</td>
</tr>
<tr>
<td>Added:</td>
<td></td>
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<tr>
<td>Package insert required two pregnancy tests prior to starting treatment</td>
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<tr>
<td>Package insert required the use of yellow qualification stickers by registered prescribers</td>
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<tr>
<td>Pharmacists required to give Medication Guide with prescription</td>
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<tr>
<td>2006 Isotretinoin Pregnancy Risk Management Program (iPLEDGE)</td>
<td>1.3 pregnancies per 1,000 female users of the program</td>
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<tr>
<td>Added:</td>
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<tr>
<td>Single, centralized program for all isotretinoin products</td>
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<tr>
<td>Required registration in database by patients, prescribers, pharmacies, and wholesalers</td>
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<tr>
<td>Mandatory monthly pregnancy tests before authorization of each prescription</td>
<td></td>
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<tr>
<td>Mandatory monthly education for patients</td>
<td></td>
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<tr>
<td>Centralized pregnancy registry</td>
<td></td>
</tr>
<tr>
<td>Removed:</td>
<td></td>
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<tr>
<td>Use of yellow qualification stickers by registered providers</td>
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</table>

*Accutane is a brand of the generic isotretinoin.  
Source: References 9 and 10.
If FDA deems that a REMS is necessary, the Agency directs manufacturers to create a REMS with specific elements and the manufacturers are required to comply. Manufacturers are responsible for implementing the system and working with FDA to assess and monitor outcomes of the system. On March 27, 2008, FDA clarified that certain medications with a previous RiskMAP were deemed to have a REMS after appropriately requirements were met. As of July 2009, approximately 50 different REMS programs were required by FDA. FDA maintains a list of currently approved REMS at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

Because each REMS is created independently by the affected medication’s manufacturer, REMS lack standardization in program design and implementation. (However, generic versions of a medication use the same REMS as the branded product.) The resulting growing number of disparate programs leads to administrative, logistical, and workflow challenges for the health care system. The inconsistency that results from such “silo” programs leads to provider confusion, administrative inefficiencies in implementation, workflow inefficiencies, and burdens on the health care system. This burden on the health care system has the potential to reduce patient access to medications because it may limit provider participation.

Participants noted that independent development of each REMS has resulted in limited opportunities for stakeholders, such as health care providers and patients, to provide recommendations regarding how to design and implement existing REMS early in the process and prior to the announcement of a REMS. The creation of a standardized system of REMS tools could facilitate opportunities for stakeholder input earlier in the REMS design and development process, help streamline implementation for stakeholders, and reduce the burden on the health care system.

FDA’s increased REMS activity since enactment of FDAAA in 2007 could affect a much broader patient population and thus have a greater impact on the health care system. This recent activity has stimulated discussion of broad-based solutions for developing a standardized system for REMS. Standardization, consistency, and program efficiency and design must be addressed to streamline the implementation and logistics of REMS programs and support achievement of intended outcomes while minimizing potential negative effects on the health care system.

FDA has recognized the need to support the development of an interoperable system that will efficiently implement the needed programs and achieve the goals of balancing access with risk. More recently, FDA has aimed to address concerns about the impact of REMS on the health care delivery system and has engaged in several activities to gather feedback, including stakeholder and public meetings, and continues to proactively seek input. Furthermore, they acknowledge the importance of feedback from front-line health care providers about their experiences with existing programs.

APhA Stakeholder Meeting on Risk Evaluation and Mitigation Strategies

To explore standardized solutions for REMS, APhA convened a stakeholder meeting on July 15, 2009. Participants included pharmacists from various practice settings, physicians, researchers, patient advocates, and a nursing delegate, as well as observation by an FDA representative (see Appendix). Goals of the meeting were to survey current experiences with risk management strategies and discuss options for developing future programs, with an emphasis on standardized, system-based solutions that will 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, systematic process for implementing REMS. This white paper presents a summary of the meeting participants’ experiences and recommendations for future steps, combined with a review of the literature on REMS and risk management that was performed by the author.

Experiences with current risk management strategies

In general, participants’ experiences with existing risk management systems led them to stress that complete elimination of risk is impossible and the benefits of any restrictive risk management program must be weighed against its burdens.

It is important to recognize that all risk management strategies can increase costs and burdens for health care providers and patients, have the potential to shift prescribing patterns to non-REMS medications that may be less therapeutically appropriate, and limit patient access to medications that require a REMS if providers choose not to participate in a REMS program or if a REMS program does not allow any willing provider to participate. Furthermore, no standardized, system-based process is in place to measure the effectiveness of any of the components or tools used in a REMS and to evaluate whether the added cost is beneficial in mitigating risk. In a recent survey of more than 2,000 practicing pharmacists, 61% stated that risk management programs had a negative impact on their practices because the programs were confusing and carried excessive costs.

In addition to the economic cost for patients and health care providers, all restrictive measures have the potential to reduce patient access owing to a lack of provider participation in a REMS because of the program’s impact. Limited provider participation could contribute to patients being excluded from therapy for otherwise treatable conditions and can lead patients to seek illicit or unproven measures to treat their conditions—strategies that carry their own safety issues. Therefore, the group agreed that the most restrictive REMS measure (i.e., restricted distribution) should be reserved for only those situations in which the measure would be critical for risk reduction to ensure patient safety.

Participants discussed their experiences with a variety of specific risk management tools used by existing REMS (some were previously categorized as RiskMAPs) and provided their recommendations for modifying such tools and overall risk management programs.
Medication guides

Medication guides (MedGuides) are one of the most common risk management tools used by many current REMS. For a REMS, MedGuides are often combined with Dear Health Care Provider letters. Although MedGuides are a frequently used tool, they are not without challenges. MedGuides create administrative burdens, workflow inefficiencies, and supply challenges for pharmacists; they also generate extra costs (e.g., paper and ink for printing), lack a balance of risk and benefit information, and have format inconsistencies. Meeting participants noted that MedGuides are generally ineffective at communicating risk information to patients.

Participants agreed that patients often do not read MedGuides, and those who do struggle to understand them. The participants felt that current MedGuides are written at a very high reading level and are challenging from a health literacy perspective. MedGuides tend to provide very lengthy technical information but do not summarize the most important points for patients or provide a list of actionable items so patients know how to apply the information, participants remarked. In addition, MedGuides lack information about the balance of benefit and risk and may contain information that is inconsistent with other written patient materials. Furthermore, existing MedGuides do not take into account patient diversity, such as cultural issues, and are often not available in languages other than English.

Additional research supports the meeting participant’s experiences with MedGuides as risk communication tools. For example, in one survey, many pharmacists reported receiving complaints from their patients that they did not understand the MedGuides. Furthermore, this survey revealed pharmacist confusion about the use of MedGuides—only 26% of pharmacists correctly responded that the MedGuides should be provided with both initial prescriptions and refills.

Another challenge that participants reported is the growing number of MedGuides and the need to keep track of which medications require a MedGuide. Concern was raised that rather than being available from one centralized location, MedGuides must be ordered from each manufacturer when the pharmacy’s supply runs out, or MedGuides may not be included with the delivery of the medication order. Therefore, participants commented that it can be difficult to ensure that the pharmacy has a supply of the most recent set of MedGuides for all covered medications, particularly when MedGuides are revised or new ones are issued. Although manufacturers are required to provide MedGuides to the pharmacy, participants noted that currently, many of the costs associated with identifying, storing, and dispensing MedGuides are borne by pharmacies (e.g., printing costs for pharmacies that have voluntarily chosen to print MedGuides to improve identification and dispensing processes). To avoid further confusion and burdens on pharmacies, participants recommended that the MedGuide system be addressed before additional MedGuides are required.

Participants discussed the need for an easy-to-read, patient-friendly version of each MedGuide that could be supplemented by a comprehensive MedGuide for patients who wanted more detailed information. The patient-friendly component could explicitly state which symptoms should be of concern to patients and when to contact the health care provider. Participants also recommended that important educational messages be provided in a face-to-face encounter with a health professional, and written material should be used as a supplement to the personal interactions. Participants noted that, ideally, the information that the patient receives from the pharmacist will reinforce what they already received from the prescriber.

Participants acknowledged that FDA and FDA’s Risk Communication Advisory Committee (RCAC) have recognized the need to improve written information that patients receive at the pharmacy, such as MedGuides, and have engaged in ongoing activity with stakeholders to address this issue. For example, the RCAC developed recommendations for better dissemination of information following a February 2009 committee meeting. In addition, FDA’s Office of the Commissioner hosted a public workshop on providing effective information to patients in September 2009 that focused on MedGuides, Consumer Medication Information, and patient package inserts.

Informed consent forms

Informed consent forms, or patient agreement forms, are generally used to ensure that patients are aware of the risks posed by a medication and acknowledge acceptance of those risks when they receive a treatment. Participants expressed concern that, in current practice, these forms are sometimes used for liability reasons rather than as a tool for patient education and empowerment. They speculated that lack of provider compensation for time spent discussing the informed consent documents may contribute to this issue. Participants believed that informed consent forms could be a tool to promote communication, empower the patient to work with health care providers, and assist in the patient education process. If informed consent forms are used as a REMS tool, a streamlined and consistent process should be used for implementation.

Participants also discussed medication therapy management (MTM), which is a patient-centered interaction and function as a collaborative process among the patient, pharmacist, and health care team. Currently, compensation for providing MTM services is provided through several sources, including Medicare Part D, several state Medicaid programs, numerous self-insured employers, and others. More information about MTM services can be found at www.pharmacist.com/MTM. Participants discussed designating an MTM visit with a pharmacist or other health care provider as a REMS tool to review the informed consent forms and ensure that patients understand their medications’ benefits and risk, patient accountability requirements, and terms of the agreements. Follow-up could take place at later visits, telephonically, or through e-mail, text, or other forms of electronic communication. Participants also noted that, if MTM is used as a mechanism for implementing REMS tools, compensation to providers will be necessary.

Laboratory monitoring for effective and safe use

Assessments of clinical indicators for monitoring safety are used by several existing REMS programs. Such requirements,
including those for clozapine and isotretinoin, often create strict limits on windows of opportunity for completing tasks (e.g., a laboratory test) and dispensing a medication. Although such programs can support conditions for safe use of the medications, they do not completely eliminate undesirable events and they create barriers to access. For example, participants reported that prescribers of isotretinoin struggle with barriers that include working within a system that does not allow for exceptions, such as a vacation supply or specific dosing regimens outside the normal parameters.

Participants noted that such REMS programs contribute substantially to the costs associated with covered medications. These costs included those for the actual testing, as well as time required to implement the program and ensure that all program requirements are met. Participants anecdotally reported that the number of isotretinoin prescribers shrank dramatically when the iPLEDGE program was implemented, in part because of the uncompensated time spent ensuring that testing was completed and components of the REMS had been met.

**Restricted distribution**

Restricted distribution programs, such as those for alosetron and cisapride, can help prevent the use of a medication by inappropriate patients, but they also may create barriers to access for appropriate patients. Furthermore, participants noticed that these programs can lead to fragmentation of care, particularly if patients are required to obtain one of their prescriptions from a centralized pharmacy and these records are not communicated to the patient’s regular pharmacy. Other restricted distribution options include requiring patients to select a single prescriber (or practice) and single pharmacy of their choosing to fill all prescriptions for the medication covered by the REMS.

Greater use of restricted distribution strategies would require enhanced communication of electronic prescription records to ensure that all prescribers and dispensers have access to complete records. Participants also suggested that national pharmacy data systems, such as those used by the Department of Health and Human Services (via the Centers for Medicare & Medicaid Services) during natural disasters (e.g., Katrina Health), could serve as a model strategy for allowing the review of prescription fill histories without limiting patients to a single location. If such a system is used for restricted distribution, attention to database design would be needed to ensure that all REMS medications, including those that are paid for in cash rather than through a third-party insurer, are captured by the system.

Participants commented that restricted distribution strategies should include options to accommodate patients who live in multiple locations throughout the year and patients who travel. The system also would need to accommodate individuals who move across practice settings (e.g., community, hospital, nursing home, assisted living). Finally, the participants emphasized that the use of restricted distribution as a REMS tool would need to be limited to cases involving only the most serious risks.

**Specialized training**

Several existing REMS programs require health care providers to undergo specialized training before prescribing or dispensing a medication. Participants noted that many providers do not participate in the additional training required by these REMS, which results in barriers to access for patients who have difficulty finding providers participating in a specific REMS program.

Finding a provider who participates in the REMS can be particularly problematic for patients whose insurance coverage has a specific network of providers. Furthermore, patients in rural areas may live several hours away from prescribers who have participated in required REMS training. In more densely populated areas, patients may live in closer proximity to participating prescribers but may have difficulty scheduling appointments.

Specialized training issues also can cause problems in pharmacies because all pharmacists in a participating pharmacy may not have received the training. Additionally, pharmacists who work in multiple locations or are not permanent staff in a participating pharmacy may not have received the REMS training. These situations could result in dispensing delays when the activities required are above the common set of dispensing procedures for a pharmacy. Pharmacists also may face administrative and logistical challenges because various pharmacies may have different operating systems, procedures for accessing REMS programs (e.g., specific login codes), and processes for handling other features of the programs. Physician group practices may experience similar issues.

**Specific ordering/inventory procedures**

In some current risk management programs, community pharmacies must use specific ordering procedures to obtain medications for patients. For example, pharmacies that dispense thalidomide must individually order the medication for a specific patient. If that patient discontinues the medication, it must be returned to the distributor rather than kept in stock for a future patient.

Drawbacks to such procedures include the time-consuming nature of handling a patient-specific medication and the requirement for additional training and administrative oversight. The associated costs can reduce pharmacy participation, resulting in fewer options for patient access.

These policies also may result in inconsistent compliance with procedures, in the event that a pharmacy inadvertently has an incorrect process in place. Individuals who may not know the procedure or who do not perform it on a regular basis may have an increased potential to experience challenges complying with the program, face administrative and logistical burdens, and require additional support. Pharmacies incur additional costs for administrative oversight to ensure that processes are implemented and maintained correctly. Thus, these factors may ultimately result in delayed patient care.

Participants urged that any requirements for specific ordering should be standardized so pharmacies would not need to learn and accommodate an ever-expanding number of differing policies and procedures.
Patient registries

Patient registries require all patients who receive a particular medication to participate in a central registry that tracks the safety of the product. Participants noted that registering all patients when the medication is used by a small population is feasible, but as numbers increase, systems become unwieldy and difficult to manage unless a streamlined, efficient system to enroll patients is developed. Even with a small patient population, registries can cause delays in treatment, particularly if a patient or provider inadvertently fails to complete a step in the process.

Participants reported that providers are sometimes unaware of appropriate processes for using a registry in current practices. Furthermore, many patient registries require duplicate entry of information, leading to inefficient use of providers’ time. Health care providers are not compensated for their time dedicated to the administrative requirements of the registry, which acts as a deterrent to participating in such REMS, particularly if the process is cumbersome.

Well-designed patient registries could support high-quality patient care, according to participants. In some instances, health care providers have supported the use of state prescription drug monitoring programs, which are used by many states to track patient prescriptions for controlled substances. Providers anecdotally reported that such systems, when used appropriately, could be beneficial because they provide a useful tool to support safe and appropriate practice and they do not require providers to spend large amounts of uncompensated time managing the system. Participants recommended exploring opportunities for coordination with existing state tools and programs; however, FDAAA does not specifically grant authority to do so.

Participants expressed that a desired feature for a patient registry is access to the registry at the point of care. They reasoned that this design would make the process more efficient and decrease the likelihood that important steps in the process would be overlooked. For example, if the provider forgets to ask the patient a question for the registry, it becomes much more difficult and time consuming to go back and get the information from the patient than it would be if the provider had worked through any questions at the point of care. Furthermore, participants recommended that patient registry systems be interoperable with other patient data systems.

Finally, participants cautioned against a system that is only accessible to patients via the Internet. Many patients lack reliable Internet access or may not be computer literate.

Prescription stickers

Stickers placed on written prescriptions by prescribers to communicate information to pharmacists have been used for various programs including one version of the risk management system for isotretinoin. In this case, stickers were placed on written or hardcopy prescriptions by the prescriber to indicate to the pharmacy that the conditions required for prescribing isotretinoin had been met. However, stickers posed administrative challenges for prescribers; for example, providers were unable to issue a prescription if they ran out of the stickers.

Looking to the future, participants recognized that electronic prescribing (e-prescribing) cannot accommodate stickers. As an alternative, they recommended a system that allows electronic communication between prescriber and pharmacy to indicate when aspects of the REMS program have been satisfied. (A physical back-up option could be used in situations where e-prescribing is not viable.)

Recommended strategies for standardizing REMS

Participants explored various aspects of programs that could be applied systematically to all REMS to reduce the variation of systems and processes. Although each medication or class of medications requiring a REMS will have unique safety issues, participants agreed that it would be possible to create a common framework so REMS programs have some universal similarities that could guide manufacturers as they develop individual programs and facilitate implementation of the programs by the health care system. This proposed framework will be particularly critical given that the number of medications requiring a REMS will likely continue to rise. The increasing use of REMS is expected to come from both new safety information about currently available medications and the potential that many medications in development could require a REMS.

Participants generally agreed that strategies deemed appropriate for medications with limited uses in a small group of patients would be unmanageable if applied to medications with broader uses in larger populations. This concern was particularly evident for REMS that are time consuming to implement. Wide-scale use of such programs could impede the health care system and create numerous barriers to care, which could extend beyond the medications covered by the REMS. Participants recommended involving front-line providers early in the process of developing a REMS to support creation of pragmatic, feasible systems. Streamlining the infrastructure of the REMS, including centralizing REMS functions and data management, could reduce overall costs by eliminating duplication of similar functions by multiple entities and reducing training and oversight costs.

Creation of REMS levels

Participants supported the concept of creating different levels or tiers of REMS, analogous to the Schedule I through V system used for controlled substances. The level would be based on the required intensity needed to mitigate the risk for which the REMS is designed and would automatically communicate the required REMS components to the health care provider. Participants discussed various options for defining REMS levels.

One option would create different categories based on the severity of risks that the REMS is designed to prevent. Standard REMS components could then be selectively used based on the required intensity of the REMS. For example, the lowest level of the system could include REMS that are composed of a MedGuide and Dear Health Care Provider letter, whereas use of restricted distribution programs would be reserved for only...
the most intensive REMS level (i.e., REMS designed to mitigate the most serious medication risks). Such a system may help support the goal of ensuring that the most restrictive elements, which create the greatest barriers, are limited to only absolutely necessary cases.

Another option discussed by the group would be to structure REMS programs according to the type of event the program is designed to mitigate. For example, specific systems could be designed for REMS intended to minimize prenatal exposure to a medication. All REMS designed to manage a medication with known teratogenic risks would be designed to use similar processes.

The group explored options for modifying REMS elements for different patient populations (e.g., institutionalized patients in long-term care settings, hospitals, or other practice settings). For example, REMS tools designed to mitigate risks for individuals to whom the medication was not originally prescribed could be modified to use less stringent requirements for institutionalized patients because these risks may be lower in such settings. Furthermore, the REMS system should have strategies in place to meet the needs of patients who have cognitive impairment or are otherwise incapable of providing informed consent or complying with other REMS requirements.

**REMS data management**

Participants recommended the creation of a standardized, system-based process for managing REMS data. They stressed the need for seamless interoperability of systems that are user-friendly, automatic, workable at the point of care, and capable of being integrated into the existing workflow for prescribers and pharmacists with minimal impact on efficiency. Furthermore, system standardization should reduce the training and administrative oversight investments that are currently required of each prescriber and pharmacy to ensure compliance with diverse systems.

The design of REMS data management systems should include interoperability with the health information technology (HIT) infrastructures currently used by pharmacy and medical practices, recommended participants. For example, a preferred system for REMS would allow data fields to be populated automatically from existing HIT records to avoid redundant data entry. Participants reported that some current software and systems can automatically retrieve appropriate patient information (e.g., patient identifiers, diagnosis codes, current medications) from a practice’s existing electronic records.

Participants noted that electronic aspects of the REMS system could be designed to support provider compliance with the logistical procedures to prescribe or dispense the medication. However, it would need to be readily accessible by all involved parties, including prescribers, pharmacists, and patients. Participants observed that the REMS system could potentially be integrated with the system for third-party claims adjudication at the pharmacy, which currently manages limited patient and prescription information electronically. Participants expected that use of such systems could improve workflow efficiencies and limit barriers to provider participation.

With national HIT standards for managing data, e-prescribing, and electronic health record (EHR) systems still evolving, the participants envisioned the evolution of an EHR system that would allow prescribers and pharmacists access to input and read data related to a REMS and to other health care issues. Current systems may need to be upgraded or revised but could potentially be used for building a new REMS system. Conversely, the REMS system will need to be flexible and interoperable with evolving HIT systems. However, participants noted that even in the future, a REMS system should not solely rely on HIT systems. A paper-based option must be available for any health care providers who have not adopted the necessary electronic technology. Finally, participants cautioned against excessive use of system alerts to support REMS requirements. They noted that providers may not closely read every alert owing to overuse of alerts causing “alert fatigue” in the use of existing systems for e-prescribing, EHR, and prescription processing.

Participants also stressed that incorporation of any REMS program requirements into existing systems must allow the REMS to be managed as part of routine prescription processing. This structure would avoid requirements for pharmacists to check REMS prescriptions through multiple unique and/or proprietary systems that are independent of the typical workflow for prescription processing. (Use of multiple unique systems poses an administrative burden, is inefficient and inconsistent, can lead to compliance challenges and inadvertently overlooking REMS requirements, disrupts workflow, and requires substantially more administrative oversight to ensure compliance.)

The necessity for strategies to manage blocks in the system to accommodate individual patient needs (e.g., a vacation occurring at the same time as a required laboratory test) or emergency situations also was discussed. Participants stressed that the system should be able to accommodate various patient situations where access to a medication may be significantly delayed because REMS requirements are not being met. A follow-up process for emergency prescriptions should be in place to record and track the causes of the occurrence and to allow for subsequent contact with other health care providers and the patient as appropriate.

Participants discussed the possibility of using a patient card program that could link into a REMS system as an option for managing data related to the REMS. If a card system were used, using a standardized system so all such cards would be managed in the same manner would be essential. Participants remarked that challenges regarding the cards include issues associated with both prescriber management of the cards (e.g., inventory issues) and patient management (e.g., lost cards).

The REMS system could include a central data repository for information that allows access and input across multiple practice settings by prescribers and pharmacists. For example, if a REMS requires laboratory monitoring, the REMS system could interface with the EHR from the laboratory with the prescriber’s office and the pharmacy.

Participants also called for centralized availability of information related to a REMS, so all users of the system (i.e., patients and health care providers) would know where to locate
such information. FDA currently maintains a website listing all medications that have a REMS and the elements of those REMS at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

Meeting participants suggested improvements that could be made to the existing FDA REMS webpage to make it more user friendly, such as including links to all of the program elements (e.g., access to printable MedGuides for REMS that require them) and providing details about the specific steps required for a health care provider to prescribe or dispense the medication. The National Cancer Institute clinical trials website (www.cancer.gov/clinicaltrials) was suggested as a model of a central repository of information from diverse sources. Furthermore, awareness among providers of the existing FDA REMS webpage is limited. Participants suggested that FDA consider setting up a dedicated website such as “www.REMS.gov” and work with stakeholders to create an educational campaign to support awareness of FDA’s resources.

**User identification.** Current REMS systems often require health care providers and patients to have different personal identifiers for each system they use. Participants discussed strategies for identifying unique users (patients, prescribers, and pharmacists or pharmacies) that could be standardized for all REMS. Such a system is needed to differentiate among individuals for cases when multiple patients with the same name (e.g., John Smith) use a medication that is covered by a REMS. Similar issues exist for health care providers who also may have identical names and require a strategy for unique identification.

The concept of developing national unique patient identifiers was discussed but was considered impractical by the group. Many current systems designed for identifying patients rely on combining patients’ names with their dates of birth or social security numbers, which are potential options for a REMS.

For providers, participants supported building on the existing identification infrastructure and using the National Provider Identifier (NPI) numbers to track provider education and eligibility to participate in REMS programs if required. The development or use of an existing process (e.g., NPIs) for user identification within a REMS system will need to take into account how to manage students, residents, and health care providers who work in more than one location.

The provider identification system will need to consider whether to use identifiers for individuals (e.g., NPIs) or to assign identifiers at the group practice or pharmacy level. Participants mentioned that in busy office practices, prescribers often instruct nurses or front desk personnel to login to manage REMS systems. Allowable uses of user identification by office staff will need to be clarified to make implementation more feasible.

**Risk management education**

Participants explored several areas of education surrounding risk management and REMS. These areas included the need to (1) address societal perceptions about medications and risk, (2) educate individual patients about appropriate use of medications covered by REMS, and (3) educate health care providers to support appropriate use of covered medications and compliance with risk management programs. **Public education campaign.** Participants expressed concern that the public lacks adequate general knowledge about balancing the benefits and risks of medications and that this situation presents a serious, broad societal issue that needs to be addressed. They noted that many patients have a low tolerance for medication-related risks and/or assume that medications are “safe” because they have FDA approval. Additionally, patients may have limited opportunities to discuss the risks and benefits of each of their medications with a health care provider (or may not realize that they should be discussing these issues with their health care provider), which can contribute to poor general understanding of appropriate medication use.

Patient-specific risk communication may be limited because it can be time consuming and is often uncompensated. Because conversations with health care professionals about medications and risk may be limited, participants noted that patients often seek information from other sources (e.g., the media) that tend to feature risks of medications without addressing the importance of balancing risk with benefit. In addition, participants commented that patients are increasingly obtaining information about their medications and disease states from Internet sources, including social networking sites and blogs, rather than more credible, authoritative sources. As a result, patients are often accessing information of questionable accuracy, which may lead to poorly informed decision making about available health care options.

Participants recommended a national public education campaign to discuss issues surrounding the balance between benefit and risk of medications and to explain how REMS can be used to influence this balance. They suggested that stakeholders, including FDA, work with the Centers for Disease Control and Prevention (CDC) or other national organizations involved in health promotion to spearhead such a campaign. Participants strongly urged that public education campaigns be continually reinforced (e.g., through individualized patient education) to produce a widespread change in patient perceptions.

In addition, participants recommended that if a REMS is added to a product already available on the market, the associated public education campaign could be designed to make patients aware of impending requirements to change their behavior and manage expectations accordingly. Such communications will be important to help frame public perceptions of REMS as risk management programs to improve patient care and safety. **Individual patient education.** Participants stated that even though individualized discussions about the different risks and benefits of medications are limited in current practice, these discussions are often necessary to support patient understanding. Participants agreed that face-to-face patient education is the most effective method for educating individual patients about their medications and is preferred to relying on written education for communicating information to patients.
Ideally, patient education would be provided by the prescriber at the point of prescribing and reinforced by the pharmacist at the point of dispensing. Alternatively, the education could be delivered in a medical home model in which a pharmacist works in a prescriber’s office or in collaboration with the office to provide education in conjunction with the prescriber. A pharmacist-provided MTM service consultation was supported as an option for providing REMS-related patient education. Participants stressed that, if a specific patient education component is required by a REMS, compensating providers for their time required to deliver the education will be critical.

Participants commented that face-to-face education helps to establish a trusting relationship between the patient and the health care provider, which can facilitate ongoing monitoring and follow-up and improve the quality of care. Face-to-face education also allows the opportunity to address any patient misperceptions and allows the pharmacist or other health care provider to tailor the education to the patient’s level of understanding and use strategies to assess and support patient comprehension. When such processes are in place, serious adverse events can be averted, resulting in cost savings. Education could be telephonic if a face-to-face visit is not practical. (The option of telephonic consultation may be needed for patients who receive REMS medications from mail order pharmacies or have limited mobility.)

Participants recommended that patient education should include discussion of medication safety issues, strategies for optimizing therapy, and patient responsibilities for complying with the REMS. The education should be individualized to meet the patient’s unique needs and care plan and provide the patient with information necessary for complying with the care plan. Patients should receive a list of specific action items, including where to go for more information and when to contact their health care team.

Furthermore, noted participants, if patients will be held accountable for complying with various aspects of the REMS, clearly communicating these requirements to them will be crucial. Patient requirements should be provided to them in an action plan during face-to-face education. For example, if patients are expected to store their medications in a certain manner, this must be clearly communicated. Education about patient responsibilities must be provided carefully to ensure that patients do not feel burdened by the process; rather, education should empower patients and help them feel that they are active partners in their own care.

Patient education and other REMS requirements should also consider issues for patients who have multiple residences and those who may transition among community, hospital, assisted living, and other institutional settings. As with provider education, a standardized, system-based approach could track patient receipt of required education and allow review of this information by providers. Furthermore, a strategy that allows modification of educational requirements should be developed for patients who have cognitive impairments or other barriers to full participation in their health care (e.g., patients residing in skilled nursing homes).

Participants suggested that education about a REMS for a newly approved medication might be implemented differently than one for a medication that had previously been on the market without a REMS. In the latter situation, the introduction of a REMS requires patients and providers to change established behaviors, whereas for a new medication, no one has an expectation based on experience of how the medication should be accessed. If a patient is well controlled on a medication, a process for maintaining the patient while the REMS is phased in could be implemented. Otherwise, patients may arrive at the pharmacy to have their prescriptions filled only to be denied the medication and experience therapy interruptions that could be detrimental to their health.

Compensation to providers for their time delivering the service is an important aspect for the face-to-face component of a REMS to be feasible, stressed participants. Participants universally agreed that face-to-face educational strategies are currently underused because no financial incentive to provide them exists. Furthermore, failure to appropriately value the time health care providers spend administering REMS programs will lead to low provider participation and barriers to patient access. Participants noted that because manufacturers are responsible for creating and maintaining the REMS, compensation for services provided by health care providers to implement the REMS could potentially be provided by the manufacturers and facilitated through user fees to a centralized entity.

Provider education. Participants underscored that health care provider training will be an essential component of new REMS systems. Recommendations for the content included a REMS program overview (including the risks to be mitigated), details about how to implement the required elements of the REMS, patient care plans and education strategies, and responsibilities of the prescriber, pharmacist, and patient. Overarching concepts in disease management could be included, not as a thorough disease state review but as a means for addressing the risk or outcomes the REMS is designed to mitigate and for explaining how the REMS could be used to support improved quality of care. Higher-level clinical and therapeutic content could be required by specific REMS, whereas education for other REMS could primarily focus on program logistics.

Content could be tailored to individual practitioner needs. A set of core elements could be developed, with flexibility to add sections to accommodate special populations, noted participants. For example, long-term care providers could elect to participate in a section of training devoted to incorporating the REMS in institutionalized settings, but primary care providers would not be required to participate in that section of training.

The design of educational components of REMS will need to account for aspects of implementation in teaching hospitals and other educational health care systems, noted participants. The process in these settings will need to accommodate prescribers (including medical students and residents who may be involved in the prescribing process) to ensure that the system works for patients in the institution or transitioning between settings.
Education about REMS should be provided in a manner that supports participation and minimizes the burden on busy health care practitioners. Participants urged that provider education required by a REMS should be accessible online, on demand, and allow users to complete the education in small segments. Adult learning strategies, including active learning and self-assessment tools, could be incorporated throughout so users could assess their own knowledge before taking the formal program assessment. The system should allow for interactivity with experts (e.g., live webinars, chats, question-and-answer boards). Educational components would need to be designed to accommodate quick updates in the event of a REMS system change, new safety information, or new medications added (for REMS designed to affect a drug class).

Participants also suggested that required REMS educational programs be linked to the proposed central REMS information repository to facilitate accessibility to potential users. Tracking of completion of educational requirements and any other REMS requirements for certification could be conducted through the repository by individual providers.

Although participants discussed the option of requiring education for license renewal as a mechanism to support widespread participation and reduce the impact on patient access, they voiced opposition to this idea. Their concerns surrounded the possibility of setting a precedent that could lead to the creation of dozens of new education requirements, which could be overly burdensome for providers and the license renewal process. If a REMS is developed for a medication used by a large population, education and/or certification should be available to any willing provider. Restrictive measures should be considered only for medications used to treat small, unique, specialized populations.

Participants recommended that verification of educational requirements could be tracked on the provider level using NPI numbers. As an alternative for pharmacists who are not required to have NPIs, the tracking could occur on a pharmacy level using the pharmacy NPI. Tracking should use a standardized system that includes training requirements for all REMS programs. Such a centralized system could track which training components were completed, if required, and which still need to be addressed for each unique user.

The group recommended that training programs be created and provided by accredited organizations that offer continuing professional education to health care providers. They recommended that various requirements could be centrally established for the REMS education to allow for consistency. Providers of continuing education (e.g., continuing medical education, continuing pharmacy education) could choose to create training programs that meet those requirements. The overall educational content, as well as specific training programs, should be evaluated by a variety of stakeholders who will be affected by the REMS. Requirements for program review also should be determined collaboratively.

Pilot testing of REMS systems

Participants acknowledged that limited data are available to guide the development of new REMS systems, regarding both the effectiveness of existing programs at preventing risks and their unintended consequences. Therefore, they supported the suggestion that new REMS strategies be pilot tested before implementation on a national scale.

A pilot program could be implemented in a selected market segment, with predefined outcomes to be monitored, to determine real-world effectiveness of the planned REMS system. Ideally, the pilot should assess whether the REMS achieves the desired outcomes and whether it produces unintended consequences and burdens on the health care system. Participants also noted that it would be essential to have practicing pharmacists, prescribers, and patient advocates involved during development and evaluation of the pilot process.

Participants generally agreed that questions remain regarding funding for REMS pilot programs. However, they suggested that manufacturers could potentially fund the pilot indirectly through user fees to a central entity. Participants recommended consideration of user fees to FDA to pilot test REMS and expressed that a reliable source of funding must be established to ensure ongoing monitoring occurs.

Identifying outcomes of the REMS system

Although there will be differences in the specific outcomes that will be tracked by individual REMS, several issues can be addressed in a systematic fashion. Participants stated that it is essential to prospectively identify the specific risks each REMS is designed to mitigate, the associated outcomes to be measured, and the strategies for measurement. Participants agreed that stakeholders from multiple constituencies should be involved in assessing why a component of a REMS was or was not successful in mitigating risk.

Participants stressed that outcomes must be achievable and acknowledged that REMS systems cannot eliminate 100% of the risk associated with a medication. Furthermore, some REMS are designed to mitigate adverse events that could potentially occur for a number of reasons, particularly in patients with multiple disease states. Thus, some occurrence of adverse events among patients using the medication should be expected regardless of any REMS system. Ideally, baseline data would be established before the REMS is implemented to accurately evaluate the impact of the REMS.

Monitored outcomes may include both those that affect the patient and those that impact other individuals. If the REMS is designed to minimize the incidence of a single serious adverse event associated with the use of a medication, tracking the impact of the REMS on the incidence of that event is relatively straightforward; however, determining which components of the REMS were responsible for the impact may not be possible. On the other hand, if a REMS is designed to address behaviors of individuals other than the patient or risks based on population-level data, accurately determining the overall impact of the REMS or the effectiveness of individual REMS tools to mitigate such risks is much more difficult.
Participants remarked that a well-designed REMS could not only reduce specific adverse events but also improve other aspects of quality of care. They recommended use of systems to assess and report on both positive and negative outcomes of a REMS. They suggested use of quality-reporting measures that would be linked to REMS development and implementation to support quality of patient care and lead to more educated, empowered patients. Monitoring for unintended consequences of the REMS was also considered crucial by participants. Such consequences could include shifts in prescribing patterns that result in greater use of non-REMS medications that may not be as therapeutically appropriate and changes in pharmacy stocking of medications covered by the REMS. To monitor for such outcomes, planned evaluations could track the rates of prescribing and adverse events associated with other medications that may be used as alternatives to medications covered by the REMS. In addition, patient attempts to access medications outside legitimate distribution channels should be monitored.

Finally, participants concurred that evaluation of REMS that require health care provider certification and training should include an assessment of the proportion of eligible providers who participate in the training and prescribe or dispense the medication.

### Table 2. Recommendations for creating a standardized REMS system

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Balance</td>
<td>The need to control medication risks must be balanced against the need to maintain access and affordability.</td>
</tr>
<tr>
<td>Standardization</td>
<td>REMS should have a standardized, system-based process that is user-friendly, seamless, and integrated into the workflow of prescribers and pharmacists (ideally as a software function that operates in the background). The system could include a central information repository that allows access and input by prescribers and pharmacists.</td>
</tr>
<tr>
<td>REMS levels</td>
<td>The REMS system could use various levels or tiers based on degree of intensity and the types of risks being targeted (e.g., REMS level 1 would be the most restrictive, whereas REMS level 5 would be the least restrictive). Products placed on more restrictive tiers would require more REMS components or education.</td>
</tr>
<tr>
<td>Public education</td>
<td>A public relations campaign should be implemented to educate the public about REMS and the balance between medication risks and benefits.</td>
</tr>
<tr>
<td>Individual patient education</td>
<td>When required by a REMS, patient education should ideally be provided face to face or could be provided telephonically. Education should occur both at the point of prescribing and at the pharmacy where the pharmacist (the medication expert) would reinforce the education that the patient should have already received from the prescriber. A pharmacist-provided medication therapy management service consultation could be used as a mechanism to provide this patient education. Written educational materials can be used to supplement the education, but should not be the only form of education. Face-to-face education and additional administrative time dedicated to managing the REMS must be compensated for any system to be practical.</td>
</tr>
<tr>
<td>Provider education</td>
<td>Provider education should be accessible to any willing provider and accommodate the needs of practitioners in all practice settings. It should focus on the REMS and the event(s) the REMS is designed to mitigate. REMS education for providers should also include program logistics and requirements for prescribing and dispensing the medications. General education about the disease state treated by the medication should be limited to a brief overview and not be the focus. Participants recommended that the education be provided by accredited providers of continuing education.</td>
</tr>
<tr>
<td>Pilot testing</td>
<td>Before implementation, a pilot program of a REMS that measures real-world effectiveness, not just theoretical efficacy, should be performed. In addition, practicing prescriber and pharmacist input should be used early on during the design of any REMS program.</td>
</tr>
<tr>
<td>Data management</td>
<td>The system for managing REMS data should be user-friendly, seamless, automatic, and integrated into health care providers’ existing workflow to support efficiency and compliance. Ideally, the system would interface with health information technology infrastructures used by pharmacy and medical practices.</td>
</tr>
<tr>
<td>Outcomes monitoring</td>
<td>Outcomes of REMS must be prospectively defined and monitored for effectiveness at mitigating the identified risk(s); an independent organization could be considered for such a role in collaboration with FDA and drug manufacturers. Monitoring needs to include potential unintended consequences of REMS (e.g., limiting patient access because of prescriber/pharmacists lack of participation in a REMS program, shifting prescribing patterns to non-REMS medications that may be less therapeutically appropriate). Outcomes should also capture reasons why a REMS was or was not successful.</td>
</tr>
<tr>
<td>Quality of care</td>
<td>A cross section possibly exists between REMS and quality measures. Systems should be designed in a manner that supports improved quality of care. Outcome monitoring should be designed to support this goal.</td>
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</table>

Abbreviation used: FDA, Food and Drug Administration; REMS, risk evaluation and mitigation strategies
Participants agreed that pilot testing the effect of the REMS on desired outcomes would be essential. However, despite efforts to design the best system possible at the outset, data should be collected on an ongoing basis to allow for continuous quality improvement. Such monitoring also can be used to support program modification if evidence of unintended consequences arises.

Data sources for outcomes monitoring
Participants noted that REMS systems could use several existing data sources, including the AERS and MedWatch systems, to assess program outcomes. In addition, FDA’s Sentinel Initiative is an active surveillance system for monitoring drugs, using electronic data from multiple sources. This system, which draws on existing data to actively monitor the safety of medical products continuously and in real time, could be used to assess REMS outcomes.

Exploring opportunities to involve the Reagan-Udall Foundation in REMS outcome monitoring was another option suggested by participants. (The Reagan-Udall Foundation is a non-profit organization created by FDAAA to identify and address unmet scientific needs in the development, manufacture, and evaluation of the safety and effectiveness of FDA-regulated products, including postmarket evaluation.) This organization could independently pool resources of stakeholders to examine the impact of REMS. Participants also recommended exploring options to have outcomes monitoring performed by the Agency for Healthcare Research and Quality (AHRQ). AHRQ aims to improve the quality, safety, efficiency, and effectiveness of health care.

Large national surveys could be useful for outcomes monitoring. Existing options discussed by participants include the CDC’s Behavioral Risk Factor Surveillance System, which is the world’s largest ongoing annual telephone health survey system. A second option is the National Health and Nutrition Examination Survey, which is a study designed to assess the health and nutritional status of adults and children in the United States. This survey is unique in that it combines interviews and physical examinations. Such surveys could be used to look for more global impacts of REMS systems.

Insurance companies could also be involved in tracking outcomes data. They maintain extensive databases of health care use and have a stake in promoting improved outcomes. In addition, various national organizations could enter into public/private partnerships to conduct surveys targeted to specific outcomes both before and after REMS implementation. Other national systems that track event data should be explored.

Additional potential data sources for outcomes monitoring suggested by participants include pharmacy and practice-based research networks. (These networks are groups of practices, devoted principally to the care of patients, that also are committed to partnering with academicians to conduct research in practice.)

Finally, participants cautioned that although national data can be a useful tool, performing subpopulation analyses to assess the impact on various groups will be important. For example, a REMS could impact patient access differently in rural and urban areas.

Concluding recommendations
Consensus on several themes emerged during the stakeholder meeting on designing a well-balanced REMS system. Participants observed that the lack of a system-based, standardized, efficient REMS system creates confusion, burdens the health care system, and creates barriers to patient access to medications. These burdens are likely to worsen as more REMS are developed in coming years and may impede the health care system’s ability to use medications appropriately.

Participants agreed that development and implementation of a systematic, standardized process for REMS programs is essential to minimizing the impact on patient access and the impact on the health care system and, ultimately, to improving the quality of care. Recommendations for moving forward included creating various REMS levels, using a public education campaign, providing face-to-face individualized patient education when needed, streamlining processes and requirements for provider education, creating a data management system that is interoperable with current systems, developing a robust system for outcomes monitoring, and pilot testing REMS programs and seeking early input from health care providers to support real-world effectiveness. Participants’ recommendations are summarized in Table 2. Participants advised that these features would be necessary for creating a system that enhances patient safety, promotes quality of care, and is feasible for the health care system.

Appendix. Participants in the APhA Stakeholder Meeting on Risk Evaluation and Mitigation Strategies

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Observer
Douglas Throckmorton, MD
Food and Drug Administration Center for Drug Evaluation and Research
DESIGNING A REMS SYSTEM

SPECIAL FEATURE

References


