REMS 101

Explaining the evolution of risk evaluation and mitigation strategies

By Marsha K. Millonig, MBA, BSPharm

PHOTOGRAPHY: TOM MERTON AND JEFF MERMELSTEIN

WE ALL KNOW MANY FOUR-LETTER WORDS CAN BE PROBLEMATIC, but who knew that four-letter acronyms could be as well? Since the Food and Drug Administration (FDA) received expanded authority for risk management of drug products in 2007, the Risk Evaluation and Mitigation Strategies (REMS) acronym hit our pharmacy lexicon, and life for the front-line community pharmacist will never be the same. This two-part article series is intended to explain the evolution of, and role REMS programs play in FDA drug product regulation, REMS components, example programs, profession-wide initiatives to shape REMS programs, and the use of REMS programs to address the nation's opioid misuse problem.

What Is REMS?

REMS stands for risk evaluation and mitigation strategy (or strategies). It can be singular or plural. REMS is the latest iteration in managing the risk related to medications. While medications have the potential to improve a patient's health, all medications have risks. Managing the risks and benefits of medications is not solely the FDA's job. Health care professionals, including pharmacists, need to continue to use best clinical practice to help patients get the most effective use of their medicines and avoid medication-related problems. As new data emerges and medications become more complex, however, new tools were needed for the

FDA to manage risk across a product's life cycle. As former FDA Commissioner Andrew von Eschenbach explained at a March 2010 industry meeting, the REMS initiative is a way for the agency to regulate a product from cradle-to-grave in the emerging world of genomic knowledge, where therapies will become more complex.

The FDA received expanded authority for risk management when Congress enacted the Food and Drug Administration Amendments Act of 2007 (PL 110–85) or FDAAA as it is commonly known, in September 2007. The law gave the FDA the authority to require REMS for pharmaceutical products considered high risk. The agency can require manufacturers to create and comply with a REMS program as part of product approval or after the product is on the market if new information and data become available. REMS programs may allow some products that would might otherwise be withdrawn to remain on the market because there are tools in place to manage the product's risk. REMS programs are legally enforceable, with monetary implications. Everyone involved in drug manufacture, handling, prescribing, dispensing, or dosing is responsible for ensuring compliance with REMS programs.

Risk management programs are not new. They have evolved and become more formalized and legally enforceable, and are growing in number and complexity (Table 1). One of the earliest risk management programs was implemented in 1990 for clozapine, used to treat schizophrenia. The drug can cause a serious, acute blood problem called agranulocytosis, where a patient's reduced white blood cell count could put them at serious risk of infection. Patients are required to have a weekly test to ensure they had not developed the condition to continue on clozapine and receive their weekly refill. The program requires mandatory patient, prescriber, and pharmacist registration.

Isotretinoin is another example of risk management program evolution. Label warnings were used to point out the risk of potential fetal damage when the drug was approved for the treatment of severe recalcitrant nodular acne in 1982. When fetal malformations continued to be reported, the FDA required an increasingly restrictive set of risk management activities, culminating with the iPLEDGE Isotretinoin Pregnancy Risk Management Program in 2006, a single, centralized program for all isotretinoin products regardless of the manufacturer. Patients, prescribers, wholesalers, and pharmacies must register in a database. Monthly pregnancy tests are conducted prior to prescription refills being authorized and patients must undergo monthly mandatory education.

Risk Minimization Action Plans, or RiskMAPs, evolved in 2005 through FDA guidance. RiskMAPs represented an informal process between the FDA and manufacturers for ongoing development and assessment of risk reduction tools and strategies. Under RiskMAPs, the agency could require manufacturers to undertake post-marketing risk reduction strategies as a condition for approving their product, but these were non-enforceable. By February 2007, 30 products had RiskMAPs. Challenges were encountered assessing RiskMAP programs, components, and tools that partially led to the enactment of FDA REMS authority and enforcement.

REMS Components

The FDAAA outlines a list of potential REMS components, which may include some or all of the following:

- Medication guide (MedGuide) or patient package insert (PPI), educational tools provided to each patient when drug is prescribed/ dispensed
- Communication plan, such as letters to health care providers/pharmacists, professional societies messaging, and professional education, to name several
- Elements to assure "safe use", referred to as ETASU, which are requirements or restrictions to optimize safe use of products
- Implementation system to monitor, evaluate, and improve elements to assure safe use
- Timetable for assessment is required, at minimum 18 months, three years, and seven years after REMS approval

The ETASUs may include:

- Training/certification of prescribers
- Training/certification of pharmacists/pharmacies
- Restrictions on where drug is dispensed
- Evidence of patient safe use conditions
- Patient monitoring
- Patient enrollment in a registry

ETASU are not to be "unduly burdensome on patient access" to the drug, according to the law. Considerations are to be given to patients with serious or life-threatening diseases, and those in rural or medically underserved areas who may have difficulty accessing services. ETASU must not be overly burdensome on the health care delivery

system and should be compatible with established systems supply chain distribution and dispensing systems.

For generic drugs, REMS components are limited to MedGuides, PPIs, and ETASU. However, if an innovator drug required a communication plan, then the FDA must require any generic drugs that are approved later to do the same. Generic drugs use a shared ETASU system with the innovator product as well, although a waiver can be granted.

The FDA must consider a number of factors in determining if a REMS is necessary, according to FDAAA, including:

- The number of people estimated to use the drug
- The seriousness of the disease or condition the drug will treat
- The expected benefit of the drug
- The expected or actual duration of drug treatment
- The seriousness of the drug's known or potential adverse events
- The incidence of the drug's adverse events in the population likely to use the drug
- Whether the drug is a new molecular entity

If the agency determines a REMS is necessary, the drug product's manufacturer has 120 days from notification to develop and submit it for FDA review. Manufacturers can file disputes for resolution with the FDA Drug Safety Oversight Board, although none have been filed. A drug cannot be sold if it is in violation of a REMS requirement and the FDA can find it misbranded under the Food, Drug, and Cosmetic Act with accordant civil penalties.

The FDA's Drug Safety and Risk Management Advisory Committee evaluates elements of each REMS program annually and must seek input from physicians, pharmacists, other health care professionals and patients about program elements. This may lead to modifications in a REMS program.

The number of FDA REMS programs is growing in number and in complexity with 149 REMS as of July 8, 2011, compared to 50 two years ago (Table 2). REMS elements that affect pharmacists the most are patient education, elements to assure safe use, and the implementation system.

Burdens and Issues for Providers and Patients

While broad REMS elements are outlined in FDAAA, each specific REMS program is developed individually between the drug's manufacturer and the FDA. As a result, there are a growing number of different programs that create administrative, logistical, and workflow challenges to health care providers and systems. These issues can lead to situations that impact patient access to medications.

Table 1. Evolution of Risk Management Strategies

Clinical trial data
Post-marketing surveillance data: • MedWatch • Adverse Event Reporting System (AERS)
Product labelling
More restrictive risk management programs • Medication Guides (MedGuides) • Restricted distribution
RiskMAPs
REMS

Issues identified at a stakeholder's meeting convened in July 2009 by the American Pharmacists Association (APhA) were many. Among them were:

- Changing prescribing practices to avoid a product requiring REMS
- Increased costs and burdens for both providers and patients
- MedGuide readability, effectiveness and distribution challenges, and informed consent form processes and uses.
- Time limits for some REMS requirements (such as lab tests)
- Impact of limited, restricted distribution upon patient access
- Training-related problems
- Different product ordering and dispensing procedures
- Impact of patient registries for products used by a large patient population (such as long-acting opioid medication)
- Prescription stickers in an era of e-prescribing

These issues have been communicated to the FDA by NCPA and other professional organizations during all steps of program development at stakeholder forums, and other venues.

When the FDA turned its focus on a class-wide REMS for long-acting and extended-release opioids in 2009, profession-wide efforts to address REMS-related burdens and issues became more intense in light of the nearly four

billion prescriptions the potential REMS could impact. The July 2009 APhA stakeholder meeting on REMS identified several strategies to streamline system development and implementation, and pointed to the need for a systematic, standardized REMS process that balances the need for medication risk management and patient access impacts (Table 1). Results of the meeting were published in a white paper in late 2009. (See sidebar on opposite page.)

Later that year, the FDA issued draft guidance with advice to manufacturers on how to design drug safety strategies and REMS programs, titled, "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. (Available at: www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.) Numerous stakeholder feedback about the burdens of growing, disparate REMS programs led the FDA to hold a meeting in July 2010 to seek more input into REMS program design, goals, implementation, and effectiveness. The agency is still evaluating this feedback.

In October 2010, a second, larger REMS stakeholder meeting was convened to discuss how to formulate sound REMS policy. Thirty-four representatives from national health care provider associations representing physicians, physician assistants, nurses, nurse practitioners, pharmacists, patient advocates, drug distributors, community chain pharmacies, drug manufacturer associations, health information technology, standards, and safety organizations participated. Staff from the FDA Center for Drug Evaluation and Research observed the meeting. NCPA was among the participants.

The meeting's goal was to move REMS programs conceptual frameworks toward a REMS system design that is effective yet not burdensome enough to impact patient access. Discussion sessions addressed effective provider interventions, improving REMS standardization and communication models, using existing technology in the provider workspace for REMS implementation, and ensuring a sustainable business model for REMS-related provider activities. A detailed series of recommendations resulted in the following areas:

- Standardize design and implementation
- Maximize effectiveness
- Optimize interventions
- Leverage technology solutions

Table 2. Number of REMS Programs Approved by the FDA (as of July 8, 2011)

REMS element	Total
Total REMS currently approved	149
MedGuide only	77
More than a MedGuide	64
• MedGuide with communication plan	46
• MedGuide with elements to assure safe use	30
• MedGuide with implementation system	26
Communication plan only	8
Products releases from REMS requirement	44

Source: FDA Web site: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

- Centralize information
- Facilitate communications
- Utilize continuing education
- Establish adequate resources and compensation

A summary of the specific recommendations may be found in the resultant document, "APhA 2011 REMS White Paper: Summary of the REMS Stakeholder Meeting on Improving Program Design and Implementation." (The document is available at www.pharmacist.com/AM/Template.cfm?Section=News_Releases2&template=/CM/ContentDisplay.cfm&ContentID=25976.) Key themes called for stakeholder collaboration with the FDA toward a more effective and efficient REMS implementation and communication approach.

Operating Within the Current REMS Framework

While advocacy efforts continue, community pharmacists must contend with today's current REMS environment. Pharmacists have increased responsibility for providing patient education in the form of MedGuides and PPIs. They must deal with REMS programs that impact prescription dispensing workflow, and the administrative issues created from additional documentation and processes. Several tips for operating in the current REMS environment may help ease the burden:

- Familiarize yourself with FDA REMS programs and bookmark their website to keep up with changes (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm).

RECOMMENDATIONS FOR CREATING A STANDARDIZED REMS SYSTEM

Balance The need to control medication risks must be balanced against the need to maintain access and affordability.

Standardization 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.

REMS levels The REMS system could use various levels or tiers based on degree of intensity and the types of risks being targeted (for example, 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.

Public education A public relations campaign should be implemented to educate the public about REMS and the balance between medication risks and benefits.

Individual patient education 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.

Provider education 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.

Pilot testing 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.

Data management 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.

Outcomes monitoring Outcomes of REMS must be prospectively defined and monitored for effectiveness at mitigating the identified risk; 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 (such as 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.

Quality of care 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.

Source: APhA White Paper 2009

- Stay abreast of the patient education materials that are part of REMS programs. MedGuides may be found at www.fda.gov/drugs/drugsafety/ucm085729.htm. This is another helpful site to bookmark. Printing a list for pharmacy technicians as part of the dispensing process may help minimize workflow disruptions. Talk with your pharmacy management system vendor to see if they can incorporate MedGuide printing with other printed patient information.
- Provide staff training and education on REMS programs that impact your pharmacy's patients.
- Promote ongoing dialogue and communication with your patients about potential side effects of their medication and provide counseling on what the medication is for, how it should be taken, and what to do if they do experience problems. Ensure that your pharmacy is designed with a private area for counseling.
- Talk with your area physicians and keep them informed on new REMS programs and create a dialogue to address issues that may impact patients affected by the programs.

The FDA released its plan for a long-acting and extended release opioid REMS on April 26, 2011. While many of the most burdensome elements that were proposed were not included, the dispensing of MedGuides is part of the plan. The new REMS plan focuses primarily on educating doctors about proper pain management, patient selection, and other requirements and improving patient awareness about how to use these drugs sfely. As part of the plan, FDA wants companies to give patients education materials, including a medication guide that uses consumer friendly language to explain safe use and disposal.

Community pharmacists have an excellent opportunity to take the lead as advocates of improved patient safety. Think about setting up your pharmacy as a pharmacy with REMS expertise—a "go to" pharmacy for patients on medications subject to a REMS. Practices that are able to effectively navigate the process for different REMS will have a competitive advantage. This is especially true in the area of pain management as you'll read in Part Two of this series in the October issue. aP

Marsha K. Millonig, MBA, BSPharm, is president and CEO of Catalyst Enterprises, LLC, Eagan, Minn. She can be reached at 651-905-9002, or mmillonig@catalystenterprises.net