October 31, 2011

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

[Submitted online at: www.regulations.gov]


Dear Sir/Madam:

The American Pharmacists Association (APhA) appreciates the opportunity to comment on the Food and Drug Administration’s (FDA) draft commitment letter with manufacturers for the reauthorization of the Prescription Drug User Fee Act (PDUFA) V to authorize FDA to collect user fees for the drug review process for fiscal years 2013 through 2017, as published in the Federal Register on September 12, 2011 (76 FR 56201).

APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 62,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings and the uniformed services. Our comments reflect the views of pharmacists practicing across the spectrum of health and patient care settings.

Consistent with our previous comments to FDA on PDUFA reauthorization, APhA supports the PDUFA program and its ability to support FDA’s drug review process and mission to promote and protect public health. APhA supports the proposed PDUFA V recommendations as they are powerful and necessary improvements to the PDUFA program.

Generally, APhA supports revisions outlined in the draft agreement related to:

- Enhanced drug application review model;
- Modifications to the user fee schedule for the drug review process to ensure adequate funding and staff for FDA to meet PDUFA performance goals;
- Extended timeframe by which FDA must approve or reject new drug applications;
- Development of a 5-year plan to further standardize FDA’s drug risk-benefit process;
• Enhancements to post-market surveillance and adverse event tracking activities through programs such as the Sentinel Initiative;
• Enhancements for managing drug applications with biomarker or pharmacogenomic details;
• Outlined strategy and time frame for FDA to continue to discuss and gather public input on improving risk evaluation and mitigation strategies (REMS) programs;
• Improved REMS standardization and integration into existing and evolving medical and pharmacy practice technologies and workflows;
• Earlier consideration, communication, and discussion of REMS in the drug review process;
• Development of guidance on assessing a REMS program effectiveness, impact on patient access, and burden on the health care system; and
• Development of guidance on how to apply statutory criteria for when a REMS is required.

Furthermore, APhA commends FDA for its repeated efforts to engage stakeholders and the public in the development of the September 2011 proposed PDUFA reauthorization recommendations over the past year and a half. We believe that the dialogue between FDA and stakeholders at the same time FDA was meeting with industry has greatly improved the reauthorization process, is reflected in the proposal, and exceeded the minimum statutory requirements for gathering public input. Importantly, throughout the process, stakeholders were given ample opportunities to discuss issues with FDA related to PDUFA in addition to other issues of interest that were outside the scope of the PDUFA program. APhA greatly appreciates the time that FDA listened to and discussed improving REMS programs while recognizing the need to improve standardization and to address implementation challenges for pharmacists, physicians, other prescribers, and wholesalers.

The following comments provide additional information on the proposal’s provisions related to pharmacogenomics, post-market safety surveillance, and REMS.

**Proposed PDUFA V Recommendations: Biomarkers and Pharmacogenomics**

APhA is pleased that in PDUFA V, FDA aims to enhance clinical, clinical pharmacology, and statistical ability to sufficiently address drug applications that specifically include biomarkers or pharmacogenomic markers. We further support the proposed recommendation that FDA hold a public meeting to discuss possible strategies to facilitate scientific exchanges on biomarker issues between FDA and drug manufacturers. In the future, we would also support efforts to ensure guidance documents and public meetings also address the need to increase awareness of pharmacogenomics-related labeling/dosing and the need to educate health care providers and patients on how pharmacogenomics can be implemented into practice to improve patient safety and outcomes.

Related to such needs, APhA released a pharmacogenomics white paper in October 2011 on how pharmacists can integrate pharmacogenomics into pharmacy clinical practice via medication therapy management (MTM) while working with prescribers and labs to improve patient care. The paper outlines the Department of Health and Human Services Personalized Health Care Initiative, FDA’s work on pharmacogenomics, and a previous 2009 APhA stakeholder workshop on this topic. Our goal is for this product to serve as a resource for pharmacists, other health care providers, FDA and manufactures as we look to manage medications impacted by pharmacogenomics. The document is attached and publically available online at [http://japha.metapress.com/media/fcpnuvlqrg902rl5hh1k/contributions/0/k/4/k/0k4k0p031682701p.pdf](http://japha.metapress.com/media/fcpnuvlqrg902rl5hh1k/contributions/0/k/4/k/0k4k0p031682701p.pdf).
Proposed PDUFA V Recommendations: Using the Sentinel Initiative to Evaluate Drug Safety Issues
APhA supports the recommendation for FDA to sponsor a series of activities to determine the likelihood of using the Sentinel system to assess drug safety issues that may require regulatory action (e.g., labeling changes, post-marketing requirements, or post-marketing commitments). Such steps could help shorten the time it takes to better understand new or emerging drug safety signals and issues. Many pharmacists and pharmaceutical scientists participate in practice-based research networks and post-market surveillance activities that produce valuable data about the safety and effectiveness of approved products that will be beneficial to Sentinel Initiative. APhA looks forward to working with FDA as the Sentinel recommendation evolves.

Proposed PDUFA V Recommendations: Standardizing REMS
APhA supports the proposed PDUFA V recommendations to standardize REMS programs. Improving REMS is a key priority for APhA and we have taken a leading role in that regard by sponsoring two stakeholder meetings that both generated informative white papers. We greatly appreciate FDA staff observing both meetings. Our goal is to be a resource for FDA, manufactures and others in helping to ensure that REMS programs achieve their intended outcomes, including maximizing the effectiveness of a REMS intervention while limiting burdens on the health care system, and recognizing the important role that pharmacists play in safe medication use as part of the health care team. APhA continues to advocate for a standardized, system-based approach that utilizes existing technologies and infrastructures that can be applicable for any REMS program. Given the importance of REMS as a mechanism to ensure patient access to those drug that would not otherwise be approved or remain on the market, it is critical that we continue to work together on improving REMS. APhA appreciates that the proposal reflects our input throughout the reauthorization discussions, including the need for standardization, integration into health care system technologies, limiting burden, and ensuring earlier REMS discussions are reflected in the proposal.

As outlined in the draft agreement, we support FDA’s aim to initiate a public process in PDUFA V to investigate approaches and begin projects to standardize REMS programs with the objective of decreasing the burden on practitioners, patients, and others in the health care setting. We support efforts to better standardize processes for determining when a REMS is required and what elements are used in a REMS. Furthermore, we support and appreciate strategy for FDA to hold public workshops and develop guidance on methods for assessing the effectiveness of REMS, integration with existing and evolving medical and pharmacy practice technology systems, the impact on patient access, and the burden on the health care system. In addition, we supports FDA’s aim to have projects focused on pharmacy systems, education, dispensing of benefit/risk patient information, practice settings.

We also support the proposal’s enhancements to ensure earlier communication and discussion between manufacturers and FDA about REMS in pre-approval meetings throughout the review process. Earlier communications between FDA and manufactures about the need for and requirement of a REMS will allow more time for manufacturers to gather input from frontline health care providers on REMS program design and implementation strategies. Such provider input during design will help manufacturers better understand the impact, practicality, and logistics of a REMS program in practice. This will lead to more streamlined, workable REMS programs that are effective while limiting burden on the health care system.

As you are aware, APhA has communicated to FDA our REMS concerns and recommendations on many occasions. Most recently, we published an APhA 2011 REMS White Paper that summarizes our
October 2010 REMS stakeholder meeting on improving program design and implementation. APhA convened a stakeholder meeting that included 34 participants representing pharmacy, medicine, nursing, physician assistants, wholesalers, standards-making bodies, health care information technology groups, and patients. The paper is attached, publically available online at [www.pharmacist.com/REMS2011](http://www.pharmacist.com/REMS2011), and builds on our REMS 2009 White Paper, also publically available online at [www.japha.org/REMS](http://www.japha.org/REMS) and previously submitted to the PDUFA docket.

As FDA considers next steps in implementing PDUFA V REMS improvements, public workshops, and guidance, APhA encourages FDA to use our resources as reference for recommendations to improve REMS, some of which are already addressed in the draft PDUFA proposal. Table 3 and several figures in the APhA 2011 REMS White Paper summarize key recommendations and highlight the need to:

- Ensure earlier REMS communications between FDA and manufacturers;
- Include input from front-line providers early in REMS design and development process;
- Standardize programs, components and processes;
- Leverage existing technology solutions in medical and pharmacy practice settings;
- Maximize effectiveness of programs;
- Optimize provider/patient interventions, including the benefit of using pharmacist-provided MTM interventions for certain REMS in which it is determined that such an intervention best meets requirements for elements to assure safe use and documentation of safe use conditions;
- Evaluate and establish adequate resources and reimbursement models for implementing REMS-required interventions so that providers do not avoid prescribing or dispensing medications because of a REMS and do not lose money providing a REMS-required intervention.
  - Payment models are needed to ensure adequate staff and resources are available to implement restrictive REMS programs, especially those requiring provider interventions.
  - Such models could range from a REMS fee structure from manufacturers based on market share for a particular REMS drug they manufacture to various forms of reimbursement from public and private payers, such as billing through Medicare Part B.
- Establish a centralized repository or clearinghouse of REMS information to improve access to and awareness of information;
- Facilitate communications and awareness of implementation requirements;
- Utilize continuing education opportunities for provider training/education about REMS; and
- Limit burden on the health care system.

Finally, APhA supports FDA’s February 2011 draft guidance on how medication guides (MedGuide) will be used in REMS programs and refocusing REMS on programs with ETASU rather than the many REMS that are currently MedGuide-only programs.

**Closing**

In closing, we appreciate the effort to have such transparency and dialogue between FDA, manufacturers, and stakeholders as reauthorization discussions moved forward. These efforts have improved the current draft; reflect issues raised by stakeholders that are relevant to PDUFA; and overall, should help improve the reauthorization process as the proposal moves through Congress. Again, APhA appreciates that the proposed recommendations reflect FDA’s aim to better align the REMS program with the practical burdens and concerns of practitioners and patients, and address the challenges with the REMS program while continuing to seek improvements.
Thank you for the opportunity to provide comments on this important issue. We look forward to continuing to work with FDA, manufacturers, and other stakeholders on REMS and to be a resource through the upcoming Congressional debate. If you have any questions or require additional information, please contact APhA’s Marcie Bough, Senior Director of Government Affairs, at mbough@aphanet.org or by phone at (202) 429-7538.

Sincerely,

Thomas E. Menighan, BSPharm, MBA, ScD (Hon), FAPhA
Executive Vice President and CEO

Enclosures
- APhA 2011 Pharmacogenomics White Paper
- APhA 2011 REMS White Paper

cc: Brian Gallagher, BSPharm, JD, Senior Vice President, Government Affairs
Marcie Bough, PharmD, Senior Director, Government Affairs
James Owen, PharmD, BCPS, Senior Director, Professional Practice
Special Feature

Integrating pharmacogenomics into pharmacy practice via medication therapy management

American Pharmacists Association

Abstract

**Objective:** To explore the application and integration of pharmacogenomics in pharmacy clinical practice via medication therapy management (MTM) to improve patient care.

**Data sources:** Department of Health & Human Services (HHS) Personalized Health Care Initiative, Food and Drug Administration (FDA) pharmacogenomics activity, and findings from the Utilizing E-Prescribing Technologies to Integrate Pharmacogenomics into Prescribing and Dispensing Practices Stakeholder Workshop, convened by the American Pharmacists Association (APhA) on March 5, 2009. Participants at the Stakeholder Workshop included diverse representatives from pharmacy, medicine, pathology, health information technology (HIT), standards, science, academia, government, and others with a key interest in the clinical application of pharmacogenomics.

**Summary:** In 2006, HHS initiated the Personalized Health Care Initiative with the goal of building the foundation for the delivery of gene-based care, which may prove to be more effective for large patient subpopulations. In the years since the initiative was launched, drug manufacturers and FDA have begun to incorporate pharmacogenomic data and applications of this information into the drug development, labeling, and approval processes. New applications and processes for using this emerging pharmacogenomics data are needed to effectively integrate this information into clinical practice. Building from the findings of a stakeholder workshop convened by APhA and the advancement of the pharmacist’s collaborative role in patient care through MTM, emerging roles for pharmacists using pharmacogenomic information to improve patient care are taking hold. Realizing the potential role of the pharmacist in pharmacogenomics through MTM will require connectivity of pharmacists into the electronic health record infrastructure to permit the exchange of pertinent health information among all members of a patient’s health care team. Addressing current barriers, concerns, and system limitations and developing an effective infrastructure will be necessary for pharmacogenomics to achieve its true potential.

**Conclusion:** To achieve integration of pharmacogenomics into clinical practice via MTM, the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery, develop a viable business model for these practices, and encourage and direct the development of HIT solutions that support the pharmacist’s role in this emerging field.

**Keywords:** Pharmacogenomics, pharmacy practice, medication therapy management, health information technology, personalized health care.

*J Am Pharm Assoc.* 2011;51:e64–e74.

Correspondence: James A. Owen, PharmD, BCPS, Senior Director, Professional Practice, American Pharmacists Association, 2215 Constitution Ave. NW, Washington, DC 20037. Phone: 202-429-7540. E-mail: jowen@aphanet.org

This publication was prepared by Susan M. Reiss, MA, Science Writer and Editorial Consultant, Arlington, VA, in conjunction with staff from the American Pharmacists Association (APhA).

Disclosure: Ms. Reiss and APhA staff declare no conflicts of interest or financial interests in any product or service mentioned in this article, including grants, employment, gifts, stock holdings, or honoraria.
Personalized Health Care Initiative

In 2006, then Department of Health & Human Services (HHS) Secretary Michael O. Leavitt saw an opportunity to advance a new kind of medical care: personalized health care (PHC). He defined PHC as “the combination of basic scientific breakthroughs of the human genome with computer-age ability to exchange and manage data.”1 The knowledge created through the completion of the human genome is enabling researchers to characterize variations in the biology of individual patients. Gene-based medicine will help create more effective treatments for large patient subpopulations and is currently being used in practice to treat individual patients.

The PHC Initiative within HHS drew together 50 existing federally supported programs to build the foundation for the delivery of PHC. These activities involve many agencies within HHS, including the National Institutes of Health, Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Office of the National Coordinator for Health Information Technology, American Health Information Community, the Agency for Healthcare Research and Quality, and Centers for Medicare & Medicaid Services (CMS). Aware that the PHC approach would require a new way of thinking, Leavitt convened a working group (i.e., the Personalized Healthcare Workgroup) to make recommendations in several key areas: information technology, scientific foundations, regulatory guidance, and translation to clinical practice.

This systems approach to health care delivery is in the process of creating tools for electronic transmission of health records and information; conducting innovative research to delve more deeply into the effect of genes on disease progression; establishing a regulatory environment that supports effective development of drugs, diagnostics, and other means to reach specific patient subpopulations; and translating genetic information to clinical practice.

One of the first priorities of the PHC Initiative was establishing a network of electronic health records (EHRs) to ensure the availability of complete patient health information. Individual EHRs give health care providers Health Insurance Portability and Accountability Act–compliant access to genetic testing data when applicable and family health histories to enable health care providers to make more effective treatment and medication decisions. Because EHRs include diagnosis, treatment decisions, and outcomes data for large populations, the information contained in these EHR networks could be potentially used to extend our understanding of best clinical practices, treatment effectiveness, variations in patient response to therapy, and safety issues and potentially through the FDA’s evolving Sentinel Initiative, a national electronic system designed to improve FDA’s ability to track the safety of drugs.2

Other health information technology (HIT) efforts include creating secure EHRs that protect patient privacy and standards for metabolic data used in drug research and clinical decision making. A number of efforts focus on integrating genetic data into clinical practice. This requires developing new software packages that incorporate genetic data to help with clinical decisions. As the tests evolve and the results become less variable, decision support tools also should evolve to reflect added consistency.

Another priority area for the PHC Initiative was to improve scientific understanding of the interplay between genetics, disease, lifestyle, and environment. Understanding the genetic and molecular disposition of diseases and chronic conditions also gives health care providers and patients tools to predict which patients may manifest a particular disease or condition. This information will allow patients and health care providers to take steps to prevent the onset of disease. If tests reveal certain disease biomarkers (i.e., chemical or molecular activity correspond-
PHARMACOGENOMICS IN PHARMACY PRACTICE SPECIAL FEATURE

Figure 1. Personalized health care building blocks

Drug manufacturers and FDA have already started incorporating pharmacogenomics into the drug development, labeling, and approval processes. Effectively transmitting genomic information to and from health care providers is challenging because of lack of awareness, privacy concerns, and the lack of a robust, nationwide electronic health care infrastructure. As progress is made in each of these areas, the potential of pharmacogenomics will be incorporated into improved patient-centered care processes resulting from the development of proactive safety tools that will be integrated into the health care system.

Recognizing the valuable role that genomics data can play in evaluating drug safety and effectiveness, FDA initiated the voluntary data exchange program (i.e., "safe harbor" agreement) in 2003. This program asked companies to submit voluntarily genomic data along with their drug submission packages. More drug companies are now including genomic and other biomarker information in their new drug applications. These more comprehensive drug applications offer the potential for more targeted patient therapies. However, FDA Commissioner Margaret Hamburg acknowledged in 2009 that "genomics represents a chal-

ing to a disease), then treatments can be started before the disease becomes entrenched. Finally, an individual’s genetic and personal health history provide a starting point for treatment decisions involving drug therapy. A patient’s genetic blueprint can provide a roadmap to determining the drugs that will offer the most effective response. This has the potential to improve patient safety and outcomes.

As PHC evolves and is integrated into practice, patients are benefiting from the application of genetic information. One of the earliest diagnostic tests developed gauges a patient’s drug metabolism. The results of a simple assay can show if a patient has a specific combination of genetic variations in two liver enzymes that alone metabolize nearly 45% of all drugs. Depending on the outcome, physicians can tailor dosages based on molecular metabolism rather than weight.

In cancer treatment, genetic testing can pinpoint patients who will benefit from certain drug therapies. For a woman with breast cancer, a diagnostic test can determine her tumor’s genetic signature. If the patient tests positive for human epidermal growth factor receptor 2 (HER-2), she can be given trastuzumab, which suppresses excess HER-2 and cuts the risk of disease recurrence by 50%.

The regulatory component of the PHC Initiative supports development of drugs, diagnostic tests, and medical products focused on specific patient subpopulations. Keeping pace with the rapid rate of scientific and medical advances is challenging to agencies charged with oversight. FDA’s Critical Path Initiative—a national strategy for transforming the way FDA-regulated medical products are developed, evaluated, and manufactured—for example, has identified 76 scientific and regulatory areas in which progress is needed to improve and expand the science base for medical product development. FDA also is working to evaluate in vitro diagnostic tests that will reveal predisposition to diseases. Bioinformatics is another important field in realizing PHC. Computer models can assist in predicting drug effectiveness and safety and arrive at those predictions using genetic factors.

A number of challenges must be overcome to fully realize the promise of PHC. First, biomedical research and HT research must continue to move forward. This requires continued funding of innovative ideas. Translating these ideas into practical activities must be a priority. Second, user-friendly clinical decision support and information management tools are needed to drive evidence-based care into clinical settings. In addition, the relations among government, industry, and academia will continue to evolve as these groups work together to expand discovery opportunities, improve safety, and lower financial risks when developing molecular therapies and diagnostics. Finally, PHC must be delivered in a sound financial way. Preventing or treating disease early provides an intrinsic cost savings. Molecular information allows for more effective, tailored treatments that could reduce costs substantially by eliminating expensive, ineffective individual therapies.

Because PHC requires integration of many components, former HHS Secretary Leavitt anticipated the time to implement the PHC paradigm would likely take a generation. What began as a federal program will transform into a collaborative effort engag-
elenge as well as a unique opportunity” for the agency. To take advantage of genomics data, FDA participates in the HHS P4H Initiative, which is aimed at creating a foundation to use pharmacogenomic data in drug development and clinical practice. Through a number of working groups, the program also establishes a framework for electronic transmission of pharmacogenomic data from current EHR databases.

FDA also is reexamining how it shares information among divisions and with other federal agencies. In 2009, Hamburg noted that “incorporating genomics into medical product review requires an interagency, multi-disciplinary effort that transcends the boundaries of an existing center.” Intra- and interagency collaboration in the areas of research, oversight, and enforcement will be a key mode of operation to managing genomic data successfully. In addition, regulatory bodies must seek input from industry and other stakeholders to discover barriers that may stall innovation and forward progress.

Because personalized medicine requires close alignment of diagnostics and drugs, FDA currently is evaluating how it reviews drugs and diagnostics. In 2004, the agency found itself scrambling when presented with a microarray device to identify variations in cytochrome P450 (CYP)2D6 and CYP2C19, which are enzymes that play a major role in drug metabolism. At the time, FDA had few scientists on staff with sufficient knowledge to fully evaluate the product. Getting up to speed on the product and its intended use took time. The agency is developing new guidance for industry in personalized medicine. One guidance document will describe the criteria FDA will use to evaluate disease biomarkers. The second guidance document will clarify the agency’s expectations for the kinds of clinical trials and levels of confidence needed to demonstrate that a diagnostic test is accurate and can be used for clinical assessments.

Because pharmacogenomic data can help clinicians tailor drug therapies to specific subpopulations of patients, the information should be readily accessible. Although hard copy package inserts that include pharmacogenomic information are useful, a more robust health information infrastructure that includes pharmacogenomic dose responses and other details would enable health care providers to make real-time and potentially life-saving decisions when prescribing medications.

For instance, breakthroughs in understanding the relationship between genetics and drug metabolism have caused FDA to issue changes to drug labels, most recently in the case of a number of approved drugs. In the case of clopidogrel, new findings demonstrating that patients with genetic variants of CYP2C19 may not effectively convert the drug to its active form caused FDA to issue a new label warning in March 2010. Similar actions based on new genetic findings have been taken for warfarin and morphine. In the case of cancer drugs such as cetuximab, new findings suggested testing patients for K-RAS mutations before starting therapy because those individuals may not benefit from the drug. This information was added to the drug label in July 2009. Changes in drug labeling are likely to continue as more retrospective studies are conducted on approved drugs and new studies are performed on emerging therapeutics.

Pharmacogenomics: Pharmacist’s role in personalizing medication therapy

As the 21st century moves into its second decade, pharmacogenomics (i.e., the use of genetic information to predict an individual’s response to a drug) will play an increasing role in drug development and clinical treatment decisions. Using patients’ genetic information to tailor drug therapy will reduce the risk of adverse events, potentially improve patient outcomes through targeted therapies and dosing, and create a more efficient, cost-effective drug development process. By transforming a one-size-fits-all approach to drug therapy into a patient subgroup or patient-specific approach, the pharmaceutical and clinical communities are one step closer to achieving the new medical paradigm of personalized health care.

Pharmacists can serve an integral role in applying pharmacogenomics into clinical practice to improve the quality and safety of health care. As pharmacogenomic applications continue to advance, the pharmacy profession has begun to define its role and address steps to effectively integrate this emerging field into clinical practice. One avenue to implementing the PHC Initiative is by integrating it into clinical pharmacy practice through medication therapy management (MTM). This service optimizes therapeutic outcomes for individual patients. As key health care providers in MTM service delivery, pharmacists assess and evaluate a patient’s complete medication therapy regimen via a comprehensive or targeted medication therapy review, rather than focusing on a specific therapy product. By gathering key pieces of information (e.g., all medications a patient is taking, including supplements), pharmacists can assess potential interactions, recommend alternative therapies to reduce medication-related adverse effects, and effectively collaborate with the individual patient’s other health care providers to improve overall care and treatment outcomes.

In diverse patient care settings, pharmacists currently are providing MTM services to help patients achieve improved treatment outcomes. Pharmacist-provided MTM provides unique new and emerging opportunities to integrate pharmacogenomics into clinical practice and actively engage in collecting, interpreting, and using pharmacogenomic data to improve patient care. As stated by former HHS Secretary Leavitt, “Pharmacists have always been on the front line in guiding consumers about the appropriate use of their medical products. With the advent of pharmacogenomics and increasingly individualized care, pharmacists will continue to have an important role in improving the quality and safety of patient care.”

At the patient–physician level, a new model is needed to advise on pharmacogenomic results because most genetic counselors are not equipped to fully assess the genetic contributions to the overall pharmacological treatment of medical conditions. Incorporating pharmacogenomics into MTM service delivery allows pharmacists to lend their expertise to the treatment planning process to optimize treatment outcomes. Because of their in-depth training specific to medications, pharmacists, working collaboratively with the prescriber and the lab, could review all of the medications prescribed for a patient and the patient’s genomic data and offer an assessment on whether a prospective drug would provide the best fit for the condition and patient. As part of a collaborative health
care team, pharmacists can optimize drug choice and dosage and, if needed, suggest alternatives to maximize therapy outcomes.

Although using pharmacogenomic information has many benefits, determining how to disseminate those data to health care providers remains a challenge. Currently available e-prescribing systems offer one venue of dissemination. However, e-prescribing platforms are generally being integrated into EHR functionality, and the integration and movement of pharmacogenomic information within the EHR as a component may offer a more viable option for the exchange of this information. To develop a pharmacogenomic component within EHR, groups that are creating pharmacogenomic data and those who will use the data must identify key pharmacogenomic elements that will be most effective in clinical treatment decisions. Although the challenge is complex, work has begun in a number of areas to bring the promise of pharmacogenomics to patients. Moving forward, the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery, develop a viable business model for these practices that encourages and promotes the use of the clinical expertise of pharmacists working in collaboration with other health care providers and labs, and encourage and direct the development of technology solutions that support the pharmacist’s role in this emerging field.

Pharmacists and HIT
The pharmacy profession has been a leader in the health care industry in electronic connectivity, establishing standards for real-time claims adjudication and other processes dating back several decades. This history combined with its strong foundation in e-prescribing platforms and evolving EHR infrastructures has positioned pharmacy for establishing a model for incorporating pharmacogenomics into EHR. Although e-prescribing offers one option for storing, transmitting, and sharing pharmacogenomic data, considerable work remains in developing and harmonizing standards to integrate the information into clinical and pharmacy records, transmitting the data between users, and creating interoperability among organizational systems. In the long run, connecting EHR through emerging health information exchanges and among various health care providers, including pharmacists, may be a more efficient and effective method for the movement of pharmacogenomic data than using e-prescribing.

In the 2006 report Preventing Medication Errors, the Institute of Medicine recommended that all prescriptions be written and received electronically by 2010. Although this goal was challenging, the pharmacy community was well equipped to move toward it. The profession has taken the lead in developing electronic formats to transmit and receive prescriptions. In 2001, the National Association of Chain Drug Stores and the National Community Pharmacists Association founded Surescripts, an e-prescribing network. By the middle of the decade, more than 90% of U.S. community pharmacies were connected and could receive prescriptions electronically. According to Surescripts, by the end of 2010, nearly 235,000 prescribers were using e-prescribing and the number of prescriptions routed electronically had grown from 191 million in 2009 to 326 million in 2010.

Federal EHR programs
The federal government has a number of programs to spur the adoption of e-prescribing tools and electronic health records through the American Recovery and Reinvestment Act of 2009 (PL 111-5). Additional federal money is available to prescribers adopting e-prescribing tools through the Medicare Improvements for Patients and Providers Act of 2008 (PL 110-275). Although current e-prescribing infrastructure may facilitate the sharing of pharmacogenomic data in the short term, viable long-term integration into pharmacy clinical practice will only be achieved if pharmacy management systems become recognized as EHR or EHR modules, contain certified common functionalities and data elements, and are incorporated within the broader EHR structure.

Stakeholder efforts
In fall 2010, the Pharmacy E-Health Information Technology Collaborative was formed by nine national nonprofit pharmacy organizations. Since that time, the Collaborative has increased in size by the addition of several key industry stakeholders as associate members. The Collaborative’s goal is to ensure that the pharmacist’s role of providing patient care services, including MTM, is integrated into the national HIT interoperable framework. The Collaborative is pursuing EHR standards for pharmacists and pharmacy providers that effectively support the delivery, documentation, and billing of pharmacist-provided patient care services across all patient care settings. Efforts are under way currently to promote the adoption of the recently balloted and approved functional profile for pharmacist/pharmacy provider EHR that will facilitate the movement of relevant patient-specific information, including pharmacogenomic data, to a patient’s entire health care team, including pharmacists, through a practice site’s information management system. Connectivity for pharmacists to the EHR infrastructure will be critical as pharmacists continue to expand their role as patient care providers and increase their involvement in the application of pharmacogenomics to improve patient care and outcomes.

Personalized health care delivery
Pharmacists will play a leading role as the health care system moves toward the paradigm of personalized health care. Through MTM initiatives, pharmacists have already been repositioning themselves as integral players in a coordinated health care approach to patients—one that emphasizes collaboration among health care providers, patients, and insurers. MTM is a comprehensive patient care service that provides valuable treatment information to all of the patient’s health care providers. MTM focuses on the entire spectrum of medication used by a single patient. This approach gives patients a coordinated approach to therapies that may not be achieved using more traditional methods. Developing standardized processes for incorporating pharmacogenomic drug data in the MTM care process will contribute to improved decision making on the proper selection and use of medications and contribute to the achievement of the best outcomes for individual patients.
Implications for the health care system

Integrating pharmacogenomic data into clinical practice will likely increase patient safety and reduce costs. It’s estimated that 1.5 million preventable serious medication errors occur annually in the United States. Those numbers translate into $177 billion spent on services associated with the corresponding illness and death. In addition, nearly 40% of the compounds in the drug pipeline are targeted therapies. A majority of these drugs will be prescribed for oncology applications and will take into account a patient’s genetic or biomarker information.

Genetic information may come from clinical trials, personal testing, and drug development. Careful collection, compilation, storage, dissemination, and protection of the information is critical. Such a system will produce an effective and efficient tool for researchers, industry, and the clinical community to use in the therapy decision-making process and will have a considerable effect on the health care system. Regulatory, clinical, and scientific personnel are collaborating to develop a knowledge base of drug therapy and pharmacogenomics that will inform decisions as information technology personnel build electronic patient management systems.

Pharmacogenomics has tremendous potential to affect patient care within the health care system positively. Addressing current barriers, concerns, and system limitations and developing an infrastructure for the future in which all health care providers can work collaboratively to improve the care of patients through the application of pharmacogenomic data in clinical practice will undoubtedly improve patient care, achieve better outcomes, and enhance health care delivery.

Exploring pharmacy’s role in pharmacogenomics: A 2009 APhA Stakeholder workshop

To explore developments in pharmacogenomics and the role it can play in clinical pharmacy practice, APhA gathered leaders at the request of HHS from pharmacy, medicine, and HIT at an APhA Stakeholder Workshop titled Utilizing E-Prescribing Technologies to Integrate Pharmacogenomics into Prescribing and Dispensing Practices, held on March 5, 2009. The stakeholder workshop provided an overview of personalized medicine and pharmacogenomics within HHS; an update on the state of HIT, EHRs, and e-prescribing; an overview of pharmacogenomics from theory to practice; and defined steps for moving forward.

Overview

The invitational meeting offered a venue for the pharmacy profession to discuss the current state of pharmacogenomics, past successes, future challenges, and the profession’s pathway forward for integrating pharmacogenomics into clinical pharmacy practice. At the outset of the meeting, participants heard the following challenges for integration: (1) genetic tests exist for only a small number of drugs and diseases, (2) clinicians and insurers want evidence that genetic tests add value to prescribing decisions, (3) a lack of familiarity with genetic information diminishes its impact on treatment decisions, and (4) a limited information infrastructure fails to provide access to an ever-expanding reservoir of genetic information to treat patients. Participants discussed how new HIT strategies might improve the flow of pharmacogenomic information between providers and pharmacists, discussed the challenges associated with integrating pharmacogenomic data with EHRs, and made recommendations to overcome those barriers.

Key stakeholder workshop presentations, discussions, and comments

An overview of personalized medicine and pharmacogenomics within the Department of Health & Human Services and the Food and Drug Administration: The science of testing

Presentations by: Gregory Downing, DO, PhD, Project Director, Personalized Health Care Initiative, Department of Health & Human Services; and Issam Zineh, PharmD, Associate Director for Genomics, Center for Drug Evaluation and Research, Food and Drug Administration

Downing discussed how advances in both genetic research and HIT have provided a foundation for pharmacogenomics. The HHS PHC Initiative was launched to expand and harness the power of these enabling technologies to improve health care safety, quality, and effectiveness. Downing described the following PHC goals:

- Continued development and expansion of the biomedical science base to address genetic aspects of disease and prevention
- Creation of a secure electronic national health information system that can store, assemble, exchange, and analyze genetic data and serve both researchers and clinicians
- Partnerships with industry to translate robust genetic and clinical research into innovative medical products and services that are safe and effective
- Integration of genetic knowledge, decision tools, and therapeutic approaches into widely used clinical practice

Downing emphasized that pharmacogenomics represents the leading edge of genomics in health care. He warned that simplistic characterization of personalized medicine would lead to unfulfilled expectations. He also suggested that opportunities exist for mass customization of technologies and tools.

Zineh. Zineh stated that FDA has “reached a critical mass of interest in personalized therapeutics.” Personalized medicine first became a priority for FDA in 2002, and since that time, the agency has been building the scientific and regulatory infrastructure needed to support the emerging field. Zineh described the voluntary genomic data submission process in which drug developers, academic researchers, and others share genetic data or other biomarker data of a particular drug with FDA for scientific exchange purposes. These data may include those on variable drug response or adverse events. This information is provided under a “safe harbor” agreement mechanism that allows for the exchange of data without regulatory consequences.

According to Zineh, FDA is taking greater initiative and asking new drug sponsors to look for genetic biomarkers that might be associated with drug response or adverse effects. Since 2004, FDA has received approximately 50 voluntary and exploratory data submissions spanning all major therapeutic areas. Over time, as genetic biomarkers are discovered and validated, Zineh predicted that a larger proportion of new drug approvals will be labeled with genetic indications or dosing recommendations. The number of investigational new drugs applications for which the Center for Drug Evaluation and Research Services Group has been consulted has nearly quadrupled since 2008. Similar growth has been seen with new drug applications and biologic license applications. Zineh suggested that many more drugs may require genetic testing to establish dosing regimens.

FDA affirms that pharmacogenomics may be the key to improving the safety and efficacy profile of many drugs already on the market, as currently available pharmacogenomic tests help predict patients who are likely to respond to drugs and those who may suffer serious adverse effects or fail to
respond. Zineh stated that signals that a drug may be a candidate for pharmacogenomic review may come from many sources, including a drug sponsor, academic researchers, and reports in MedWatch or FDA’s own literature reviews. For example, FDA’s collaboration with Medco is expected to help assess the pharmacogenomic safety and efficacy of many currently marketed drugs. In deciding whether to recommend or require pharmacogenomic testing on a drug label, Zineh said the agency considers the severity of potential drug-related adverse events and whether they are likely to be rare or certain for specific genotypes.

Currently, clinicians do not commonly order and insurers do not regularly pay for pharmacogenetic testing, even when genetic biomarker information is on a drug label, according to Zineh. Physicians and payers want evidence that using genetic testing in treatment decisions produces a better outcome than conventional prescribing practices. However, that assessment presupposes a body of clinical evidence on which to base such comparisons.

Determining the level of evidence needed to recommend genetic testing is an area of debate. FDA urges the health care community to consider a “realistic” level of evidence in the area of pharmacogenomics. Zineh urged that this emerging field not be held to higher standards of evidence than other health care services. He also referred to a published report finding that only 15% of clinical practice guidelines are based on rigorous clinical evidence; the rest are based on expert opinion.

In closing, Zineh asked participants to consider how HIT could help advance the practice of “precision medicine.”

Discussion. In the discussion following Zineh’s talk, a majority of participants expressed surprise at the number of drugs in the pipeline that are likely to have pharmacogenomic information in the label. Participants discussed the standard of evidence that should accompany specific pharmacogenomic applications into the clinic. Many observed the need to move away from randomized controlled trials (RCT), noting that although RCTs are the gold standard to examine questions of efficacy, good epidemiologic study designs based on existing data could be important in identifying genetic risk factors for drug safety. As an example, the decision to relabel carbamazepine for genetic risk of Stevens-Johnson syndrome was based on evidence from 60 or 70 people who suffered the reaction and shared a similar genetic ancestry. Participants agreed that relabeling drugs based on genetic data would be greatly accelerated if researchers could query large clinical data sets that include both genetic and drug history information.

Participants also noted that the availability and likely proliferation of genetic tests to predict drug safety and efficacy adds another layer to prescribing decisions and amplifies the need for better tools and structures to support clinical decision making. The challenge, participants agreed, is to develop information structures that streamline and improve the decision-making process. Orderly introduction of pharmacogenomics into the clinical setting will require knowledge and information technology to converge.

Others suggested that convincing demonstration projects would be helpful, and all agreed that education and payment policies aligned to support pharmacogenomics will be needed. Downing noted that CMS is beginning to move in this direction and is exploring issues surrounding clinical use of genetic tests in order to develop policies that will guide coverage decisions.

Summary. Genetics research will drive new approaches to diagnostics and treatment focused on key patient subpopulations rather than a one-size-fits-all approach. To ensure access to and continued development of genetics-based research and related technologies, HHS launched the PHC Initiative. FDA is developing a regulatory framework to process genetic drug data, which industry is willing to supply. Determining the level of evidence needed for clinical applications of pharmacogenomic data is a matter of debate. The challenge is to develop structures to streamline and improve the decision-making process for both drug approval and clinical application.

Update on the state of health information technology, electronic health records, and e-prescribing: Transitioning pharmacogenomics to e-prescribing and electronic health records

Presentations by: Ken Whittemore Jr., BSPharm, MBA, Senior Vice President of Clinical Practice Integration, Surescripts; Lynne Gilbertson, Vice President of Standards Development, National Council of Prescription Drug Programs; and David Collins, Director of Healthcare Information Systems, Health Information and Management Systems Society

Beginning in 2004, the U.S. government began a focused effort on developing a nationwide EHR platform. An executive order by then President George W. Bush created the position of National Health Information Technology Coordinator, and the White House urged access to EHRs for all Americans by 2014. The final numbers for a 2008 National Center for Health Statistics study showed that 21% of all U.S. office-based physicians used an EHR system. Preliminary results for the 2009 study showed a jump to 27.19

As a result of stimulus funding from the American Recovery and Reinvestment Act of 2009, $2 billion in grants and loans were provided to the Office of the National Coordinator for Health Information Technology to encourage adoption of HIT. An additional $17.2 billion has been set aside for Medicare and Medicaid to reward hospitals and physicians for using electronic systems.

Whittemore. Whittemore described e-prescribing as the complete, bidirectional, electronic transmission of prescription information. He estimated that e-prescribing saves pharmacies $1.07 per new prescription and $.42 per refill. Of greater importance is the role e-prescribing can play in delivering better care to patients. For example, e-prescribing network systems can consolidate prescription histories from multiple pharmacies, both community and mail service, into one patient record to make potential interactions more obvious.

Whittemore also noted that physician participation in e-prescribing system networks has grown exponentially, in part because of Medicaid and Medicare incentives. Roughly two-thirds of e-prescriptions handled by Surescript, an e-prescribing network, are generated by EHR systems, and even small practices without EHRs are using freestanding e-prescribing systems to provide this functionality.

He noted that although pharmacogenomic information can be transmitted in e-prescriptions, work is needed to develop and harmonize standards to integrate information into clinical and pharmacy records. A dialogue between the pharmacy community and information technology developers would allow development of data elements and format for pharmacogenomic information and determine how those data will be used. Will it be given as information only, as part of the continuity of care record (i.e., a standardized format for the electronic exchange of health information), or as part of an automated drug use review process? After the standards are in place, technology vendors must incorporate them into their products, but this will occur only if they see a demand from physicians and pharmacists for pharmacogenomic data as an integral part of prescribing and dispensing medication.

Gilbertson. Current e-prescribing system standards continue to evolve. The industry standard for electronic exchange of information between physicians and pharmacists is SCRIPT. Gilbertson said that the standard, which is maintained by the National Council for Prescription Drug Programs...
(NCPDP), includes prescription and refill information, sections on drug history, medication alerts, drug allergies, and compound ingredients. NCPDP is working on enhancing SCRIPT to enable physicians and pharmacists to exchange clinical information about a patient through follow-up questions and answers. New features also will automate prior authorization, predetermination of benefits, and patient financial responsibility when the medication is dispensed.

Meeting participants noted that including clinical information in the e-prescribing platform provides a foundation for integrating pharmacogenomic data into clinical and pharmacy practice. A pharmacogenomic profile could show the patient’s drug metabolizer status or trigger medication alerts that could reduce the risk of adverse reactions. Components such as automated preauthorization also will improve workflow for the pharmacy system. As more pharmacogenomic data are provided for individual drugs, the need for prior authorization before dispensing the drug is likely to increase. An e-prescribing component that obtains information directly from a physician or patient’s EHR regarding whether a genetic test has been performed and the test results would reduce costs and administrative burden on the pharmacy system considerably.

Collins. To achieve an integrated HIT system, Collins suggested that pharmacy providers, clinicians, HIT professionals, and vendors define how pharmacogenomic information will be represented and stored in both clinical and pharmacy records and what level of interoperability will meet clinical and administrative needs. He said that by statute, EHRs must include not only patient demographic and clinical health information but also clinical decision support, physician order entry, and the ability to exchange electronic health information with other sources. By integrating these features with pharmacogenomic data into national EHR standards from the outset, a more robust system will be achieved. All of these actions must occur in a timely fashion because the deadline for a national EHR system is 2014, with gradual phase-in of adoption over the next several years.

Discussion. Following Collins’s presentation, participants discussed whether the larger hurdle is integrating EHRs into health care or integrating pharmacogenomics into EHRs. Some standalone e-prescribing systems have no means of integrating and sharing laboratory test results and cannot support pharmacogenomics. In some cases, users of large EHR systems urge their vendors to create specific applications or they do it themselves.

Harnessing the power of the growing body of pharmacogenomic data will remain difficult until the data are standardized into a form that is easily retrievable and analyzed. Creating a powerful decision-making tool for clinical practice requires a strong health care information infrastructure. At a national level, much emphasis has been placed on developing an EHR platform that would include a patient’s demographic and clinical health information, as well as clinical decision support, physician order entry, and the ability to exchange information throughout the health care community. In their current form, EHR systems cannot provide the analysis and functionality needed to incorporate pharmacogenomics into treatment decisions.

Summary. E-prescribing is becoming a common tool in the health care community. Standards harmonization remains a challenging area, and ongoing work is needed to collaborate to develop EHR and e-prescribing platforms. E-prescribing platforms provide a key foundation for integrating pharmacogenomics data into clinical pharmacy practice. Pharmacogenomic components should be built into EHR systems from the outset.

Pharmacogenomics from theory to practice: Integrating pharmacogenomics into clinical practice

Presentations by J. Russell Teagarden, BSPharm, MA, Vice President of Clinical Practices & Therapeutics, Medco Health Solutions; Mary W. Roederer, PharmD, CPP, Research Assistant Professor, Eschelman School of Pharmacy, University of North Carolina; Grace Kuo, PharmD, MPH, Program Director, Pharmacogenomics Education Program, Skaggs School of Pharmacy, University of California, San Diego; and Kevin Donnelly, Vice President, SNOMED Terminology Solutions, College of American Pathologists

Roederer. Knowing how to interpret pharmacogenomic data will become central to prescribing situations in the near future for physicians and clinical pharmacists, according to Roederer. Although only a handful of drugs now include notices about genetic testing prior to prescribing the drug (Table 1), new notices likely are on many more drugs in the future. This is a result of heightened awareness of the impact of genetics on drug metabolism. Roederer noted that hematology and oncology are two areas leading the way in which genetic information is used to guide therapy. As discussed above, warfarin and clopidogrel are two of the most well-known examples in hematology.

<table>
<thead>
<tr>
<th>Table 1. FDA requires, recommends, or provides information on genotyping for the following drugs and biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (CYP2C9, VKOR)</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin; HER2-neu)</td>
</tr>
<tr>
<td>Imatinib mesylate (Gleevec; C-kit mutations, BCR/ABL translocation)</td>
</tr>
<tr>
<td>Maraviroc (HIV-CCR5 receptor site)</td>
</tr>
<tr>
<td>Celecoxib (CYP2C9)</td>
</tr>
<tr>
<td>Cetuximab (EGF receptor)</td>
</tr>
<tr>
<td>Azathioprine and mercaptopurine (TPMT deficiency)</td>
</tr>
<tr>
<td>Irinotecan (UBT1A1; homozygous for the *28 allele)</td>
</tr>
<tr>
<td>Carbamazepine (HLA-B*5101)</td>
</tr>
<tr>
<td>Gefitinib (EGF receptor mutations)</td>
</tr>
<tr>
<td>CYP10D and CYP2C19</td>
</tr>
</tbody>
</table>

Abbreviations used: CYP, cytochrome P450; EGF, epidermal growth factor; FDA, Food and Drug Administration; TPMT, thiopurine methyltransferase.
Source: Mary Roederer, Eschelman School of Pharmacy, University of North Carolina, Chapel Hill.

Roederer discussed that although pharmacogenomics is slowly beginning to show its promise in clinical situations, it faces several hurdles. These include (1) actually ordering a pharmacogenomic test, (2) obtaining test results quickly, (3) ensuring that the results are accurate, (4) determining the level of evidence required to support the results, and (5) obtaining reimbursement for the test.

The actual use of pharmacogenomic data is spotty at best across specialties. For example, Roederer noted that in oncology, the medical community generally has not recommended that RCTs show the usefulness of genetic testing. However, when evidence is available for the tests in trials and the evidence has shown that they can affect treatment outcomes, the medical community has used the information in clinical practice. The case for genetic
testing and use in treatment decisions is unclear in the case of tamoxifen, which is a commonly prescribed drug shown to assist in limiting breast cancer recurrence. Studies have shown that patients who are low metabolizers do not experience the same positive effects from the drug as those who are high metabolizers. In 2006, an advisory committee recommended adding genetic testing information to the label; however, because the committee could not agree on whether testing should be recommended, FDA did not change the label.22

Another challenge to implementing pharmacogenomics in clinical settings is obtaining genetic information quickly. In the case of warfarin, to guide dosing, a laboratory must be able to provide genetic data on drug metabolism within 24 hours. A report in Seizure suggested that POLG DNA sequencing should be performed before administering valproic acid for pediatric seizures disorders, in order to reduce the odds of liver failure.23 If this become a standard of care, clinicians will need a fast turnaround on the DNA sequencing test.

From the perspective of her clinical practice and experience in the application of pharmacogenomic data, Roederer explained that the small number of genetic tests currently available and validated by FDA makes ensuring results a challenge. Most of the tests currently used are provided by the laboratories that developed them and most of these tests are not formally reviewed by FDA. After the test results are available, interpreting them is a lengthy process that requires knowledge of the test itself, the interplay of the genetic variants and the drug, and the patient’s clinical situation.

Increasing education about pharmacogenomic testing and the clinical applications is critical because in the area of oncology drugs, for example, therapies are effective in only about 25% of the population receiving them. Arthritis drugs have a 50% effectiveness rate and asthma drugs about a 60% effectiveness rate.22

Teagarden. Several factors will drive the standardization and integration of clinical pharmacogenomic data within EHRs and e-prescribing systems, according to Teagarden. The first is a greater emphasis on pharmacovigilance. Access to genomic data allows providers/payers to analyze trends in adverse drug reactions and flag potential connections to genetic mutations. In addition, he noted, genetic information readily available in patient records hastens identification of potential gene–drug interactions. A second factor to drive incorporation of pharmacogenomic information into health records is a growing interest among patients in learning their genetic background and having it available to health care providers. Finally, as clinical decisions rely more on genetic information, electronic support systems will have to store, analyze, and adapt to new and evolving genetic data. As genetic testing becomes more routine—as part of well visits and patient history—it should be incorporated into the patient’s EHR.

Teagarden stated that a collaboration between Medco and the Mayo Clinic has shown that genetic testing and follow-up counseling to patients helped avoid adverse reactions and save money, according to Teagarden. As part of the initiative, which involved 105 payers and 6 million covered lives, Medco offered genetic testing through its partner LabCorp to any patient who submitted an initial claim for either warfarin or tamoxifen. If test results showed a mismatch between the patient and the drug or prescribed dose, the patient’s physician was notified.

Kuo. The medical community is at a disadvantage when it comes to knowledge about genetic research and development because of its relative newness and the volume of research available. Kuo discussed that programs at medical and pharmacy schools across the country are needed to provide education resources on pharmacogenomic theories and clinical applications. Kuo noted that many observers believe that the key rate-limiting step in clinical integration of pharmacogenomics is the cursory exposure to medical genetics that most health professionals receive during their training.

Kuo described a pilot program (PharmGenEd) that was developed at the Skaggs School of Pharmacy, University of California, San Diego. PharmGenEd provides a suite of tools, including continuing medical education courses, Internet-based lectures, curricular modules for pharmacists, and presentations at professional meetings. Through these learning aids, the developers are seeking to familiarize health professionals with the challenges and opportunities that genetic tests offer to clinical treatment situations. The program aims to demystify pharmacogenomics. PharmGenEd is attempting to reach 100,000 pharmacists, physicians, student pharmacists and medical students, and other health professionals. The program is supported by CDC and works closely with national pharmacist and medical associations.

Donnelly. One aspect of a pharmacogenomic information component could be an electronic tool that would organize and relate all the systems within the human body to all of the drugs that can influence those systems, Donnelly noted. Such a tool would assist clinicians in making use of increasingly complex pharmacogenomic data in clinical situations. Building in a matrix-of-interactions tool would deliver much needed support in making individual treatment decisions.

As developers plan EHR systems, they must build in flexibility so that the system can adapt to include new information resulting from research advancement. If evidence is available to support changes in drug labeling through the application of pharmacogenomic information, this information should be included in the EHR system and supported by clinical decision support tools so that clinicians can review the information and use it in conjunction with FDA labeling recommendations.

Summary. One of the key challenges integrating pharmacogenomics into practice is educating the entire spectrum of health care providers about pharmacogenomics, the technologies of pharmacogenomics, and how to develop and apply the technologies. Despite the promise of pharmacogenomics, few practitioners use genetic data in treatment decisions. The limited availability of validated genetic diagnostics that rapidly return results makes obtaining data difficult. Two factors that will drive demand for testing are pharmacovigilance and patient demand for genetic data. Better education and decision support tools will help the health care community embrace pharmacogenomics in clinical settings.

Defined steps for moving pharmacogenomics in clinical practice forward

Workshop participants agreed that pharmacists and physicians must deliver a unified plan to HIT developers and vendors that underscores the need for clinical record and e-prescribing systems to incorporate pharmacogenomic information and related decision support tools. Achieving these goals will require clinicians and pharmacists to work with standard-setting bodies. The pharmacy and medical communities will need to make a cogent case for the benefits of pharmacogenomics because HIT developers and standards organizations must balance a myriad of requests for the EHR system.

In addition to education, participants at the stakeholder workshop identified the following action items for potential users of electronically transmitted pharmacogenomic data.

Practitioners should:

■ Identify what pharmacogenomic data are needed to make relevant clinical decisions, who should have access to the information, and what level of detail should be shared among providers.

■ Resolve issues related to who (physician or pharmacist) will handle interpreting and applying genetic test data to medication management.

■ Work with HIT vendors on standardized transmission of genetic and pharmacogenomic data.

■ Convey the need for secure electronic transmission of genetic/pharmacogenomic data to HIT vendors.
SPECIAL FEATURE PHARMACOGENOMICS IN PHARMACY PRACTICE

Facilities should:
- Use broadband to enable better information exchange among health care workers and patients.
- Update software/hardware to support data exchange.
- Adopt guidelines, policies, and procedures related to privacy, confidentiality, and ethics.
- Consider policies that align system gains with individual practitioner efforts.
- Integrate pharmacy point-of-care genetic testing, ensuring that data are readily retrievable and easily shared.

Patients/consumers should:
- Obtain a baseline level of understanding of pharmacogenomics.
- Engage in an informed understanding of privacy/security risks and protections.
- Appreciate the benefits of pharmacogenomics.
- Discover mechanisms for patients to order valid tests directly from labs.

Payers should:
- Run return-on-investment analysis, including credible third-party cost-effectiveness analysis for pharmacogenomic tests/drugs.
- Identify "low-hanging fruit" in pharmacogenomics applications that can improve patient outcomes and save money.
- Align financial/reimbursement incentives/disincentives for adoption.
- Offer team/outcome-based payment reform rather than a “silo-based” provider payment model.
- Remove payers from the clinical decision process.

Regulators/standards development organizations should:
- Develop point-of-care testing guidelines/protocols/standards.
- Request pharmacist input and access to EHR standards development.
- Conduct demonstration projects.
- Expand labeling to require pharmacogenomics information where available (include data in Investigational New Drug applications).
- Harmonize standards, terminologies, and their uses.
- Not regulate the clinical use of pharmacogenomics;
- Facilitate professional organizations to develop appropriate guidelines and requirements.

Vendors should:
- Deliver integration, interoperability, and seamless incorporation into practices/facility workflow.
- Build decision tools for prescribers.
- Comply with HITSP (Health Information Technology Standards Panel) and other relevant standards and participate fully in the interoperability development process.
- Publish industry guidelines for “floor” requirements of professional tools.

Education organizations should:
- Encourage innovative practice models that use genomic information in clinical decision making.
- Disseminate lessons learned, barriers, and successes.
- Integrate pharmacogenomics into clinical and didactic education throughout curricula (e.g., PharmD, MD, DO, RN).
- Include interprofessional training and practice models at the degree, residency, and fellowship levels.
- Integrate pharmacogenomics into community-based public health programs.

Research and development should:
- Create better clinical diagnostic support tools.
- Use clinical outcome and pharmacogenomic information for rare disease discovery and research and development on new drug targets.
- Develop trials to answer the question of what clinicians should do with pharmacogenomic information (e.g., avoid a particular drug, increase/decrease dose).
- Assist industry in determining exactly what to build first: what do we want?
- Increase funding for health systems research, including education methods and population health monitoring.
- Develop a matrix to capture genomic information relevant to each drug and related to drug–drug interactions for all pertinent classes of drugs.

APhA2010 House of Delegates adopted policy
To further promote the importance of pharmacogenomics in personalized medicine, the APhA House of Delegates adopted the following policy at its March 2010 meeting in Washington, DC.

Pharmacogenomics/personalized medicine
1. APhA supports evidence-based personalized medicine, defined as the use of a person’s clinical, genetic, genomic, and environmental information to select a medication or its dose, to choose a therapy, or to recommend preventive measures, as a means to improve patient safety and optimize health outcomes.
2. APhA promotes pharmacists as health care providers in the collection, use, interpretation, and application of pharmacogenomic data to optimize health outcomes.
3. APhA supports the development and implementation of programs, tools, and clinical guidelines that facilitate the translation and application of pharmacogenomic data into clinical practice.
4. APhA supports the inclusion of pharmacogenomic analysis in the drug development/approval and postmarketing surveillance processes.
Conclusion

All drugs are not created equal, neither are the patients who use them. Shifting the health care paradigm from one that is reactive to one that is proactive, preemptive, and personalized will take money, research, and collaboration. Transforming the current enterprise to a patient-focused, participatory endeavor will benefit patients, providers, and payers. As with all beginnings, the final path remains undecided but the goal is clear. Personalized health care can reach patients through improved understanding of the interaction between genetics and drug metabolism. After these connections are made, regulatory bodies such as FDA must act on the information and convey it to health care providers. Pharmacists providing MTM, working in collaboration with physicians, can tailor drug therapies to patient subpopulations and individuals through the effective application of pharmacogenomic data. Pharmacists have the potential to become integral players in the personalized health care paradigm. Their keen awareness of drug–drug interactions and drug metabolism make pharmacists indispensible resources when considering treatment choices. If a patient with a genetic variant is at risk for adverse drug effects, the pharmacist can suggest dosage adjustments, alternative drugs, or anticipate and manage potential adverse effects.

To achieve the integration of pharmacogenomics into clinical practice via MTM, the pharmacy profession must define a process for the application of pharmacogenomic data into pharmacy clinical practice that is aligned with MTM service delivery, develop a viable business model for these practices that encourages and promotes the use of the clinical expertise of pharmacists, and encourage and direct the development of technology solutions that support the pharmacist’s role in this emerging field. To maximize the pharmacist’s contributions to pharmacogenomic applications, continued work by the profession in these key areas is important.

Through the electronic interchange of pharmacogenomic data across an EHR that is harmonized and interoperable among all health care providers, including pharmacists, the application of pharmacogenomic data into clinical practice will improve efficiency, reduce costs, and, most importantly, achieve a more personalized treatment approach and better outcomes for each patient.

References


14. PL 111-5, §13, Division A, Health Information Technology, and §4, Division B, Medicare and Medicaid Health Information Technology.

15. PL 110-275, §132.


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

A reprint from the Journal of the American Pharmacists Association
**APhA 2011 REMS white paper: Summary of the REMS stakeholder meeting on improving program design and implementation**

**American Pharmacists Association**

**Abstract**

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

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

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

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

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


The American Pharmacists Association (APhA) prepared the background materials for the stakeholder meeting and white paper. Susan M. Reiss, MA, Science Writer and Editorial Consultant, Arlington, VA, prepared this white paper as a paid consultant for APhA.

**Correspondence:** Marcie Bough, PharmD, American Pharmacists Association, Washington, DC 20037. Phone: 202-429-7538. E-mail: mbough@aphanet.org

**Disclosure:** APhA staff and Ms. Reiss declare no conflicts of interest or financial interests in any product or service mentioned in this article, including grants, employment, gifts, stock holdings, or honoraria.

**Funding:** The APhA 2010 REMS Stakeholder Meeting and this white paper were supported by Amgen Inc., Catalina Health Resource, King Pharmaceuticals Inc., LearnSomething, and RelayHealth; by an educational grant from Lilly USA LLC; and by independent educational grants from Boehringer Ingelheim Pharmaceuticals Inc., Endo Pharmaceuticals, Purdue Pharma LP, Pfizer, and Teva Pharmaceuticals.
At a Glance

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

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

Proceedings

This white paper discusses the formulation of recommendations for improving REMS programs. The document is organized in the following sections:

- REMS background (page 341)
- APhA 2010 REMS stakeholder meeting (page 343)
- Goals of the stakeholder meeting (page 343)
- Discussion I: Effective provider interventions (page 344)
- Discussion II: Improving REMS standardization and communication models (page 348)
- Discussion III: Using existing technology in the provider workspace for REMS implementation (page 350)
- Discussion IV: Ensuring a sustainable business model for REMS-related provider activities (page 352)
- Recommendations (page 354)
- Overall summary (page 356)
- Appendix 1: Food and Drug Administration (FDA) activities related to REMS (page 356)
- Appendix 2: American Pharmacists Association (APhA) activities related to REMS (page 357)

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

REMS background

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

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

Existing REMS framework

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

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

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

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

Table 1. Existing REMS framework per FDAAA requirements

<table>
<thead>
<tr>
<th>Required REMS elements</th>
<th>Timetable for assessment of the REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A REMS may include these elements:</td>
<td>Medication Guide</td>
</tr>
<tr>
<td>Communication plan for health care providers</td>
<td>Implementation system</td>
</tr>
<tr>
<td>ETASU</td>
<td>ETASU may include these elements:</td>
</tr>
<tr>
<td>Certification and specialized training of prescribers, pharmacies/pharmacists, and other dispensers</td>
<td>Restricted distribution of a drug to limited settings</td>
</tr>
<tr>
<td>Dispensing to a patient based on evidence or other documentation of safe use conditions, such a lab results</td>
<td>Patient monitoring and/or patient registry</td>
</tr>
<tr>
<td>Prescriber and/or pharmacist registry</td>
<td>Abbreviations used: ETASU, elements to assure safe use; FDAAA, Food and Drug Administration Amendments Act of 2007; REMS, risk evaluation and mitigation strategies.</td>
</tr>
</tbody>
</table>

Source: Reference 1.

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

Table 1 describes the FDAAA REMS framework. According to the statute, ETASU should not be unduly burdensome on patient access to the drug and should take into consideration patients with serious or life-threatening diseases or conditions; and patients who have difficulty accessing health care (e.g., patients in rural or medically underserved areas). In addition, ETASU should be designed to minimize the burden on the health care delivery system, conform with elements to assure safe use for other drugs with similar, serious risks; and be
Table 2. Number of REMS programs approved by FDA as of March 9, 2011

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

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

Source: Reference 5.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Discussion I: Effective provider interventions**

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

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

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

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

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

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

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

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

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

Participants suggested that patient-centered services such as MTM could be useful in integrated care models for REMS implementation because of the patient–provider intervention and emphasis on patient safety. Participants discussed how REMS programs could be designed with MTM as the ETASU specific to dispensing based on safe use conditions. Through their coordinated approach to patient care and defined provider roles and responsibilities, patient-centered service models like MTM offer important patient and medication oversight as part of an ETASU in a REMS program. Participants also discussed MTM having the further advantage of being a patient intervention that can adapt over time and be tailored individually to a patient’s needs over the course of therapy.

There was general agreement that MTM services could be integrated into REMS programs as an ETASU tool if a manufacturer and FDA determined that the best way to ensure patient safety and mitigate an identified risk is through personal consultation with the patient. MTM services also could be used to document and report outcomes, a component participants noted is critical because few data exist to determine the success or failure of REMS programs. The group suggested that data created through MTM may be one way to initiate independent monitoring of adverse reactions to specific drugs as part of REMS programs; however, appropriate resources would be needed to implement data collection and analysis. In addition, a viable compensation model must be created to support these activities. (For additional discussion regarding compensation for implementing patient interventions such as MTM as part of a REMS program, see discussion in this white paper.)

Participants noted that by incorporating MTM services as a REMS tool, REMS programs would build on the successes and existing experiences with implementing MTM programs (e.g., the Medicare Part D prescription drug benefit MTM program; other public, private, and employer-based MTM programs) rather than developing an entirely new tool. (For more information on MTM, go to www.pharmacist.com/MTM.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion II: Improving REMS standardization and communication models

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Standard elements. In general, participants agreed that REMS systems should use existing standards and technology in practice settings. They also discussed the benefit of building REMS compliance requirements into EHR functionality at the point of prescribing. Participants also discussed efforts of standard setting organizations, such as the National Council for Prescription Drug Programs (NCPDP) or other accredited bodies, to develop processes to route REMS queries. Generally,
REMS queries and verification functionality ("pinging" against a REMS administrator database) could be accommodated by existing systems. Software that routes the verification queries, documentation, or other activities to and from a REMS administrator database to appropriate entities may require slight modifications but can work seamlessly within the existing pharmacy claims processing infrastructure.

There was general agreement among participants that standardization could help to assess whether various risk management strategies are effective. Currently, data showing whether REMS programs make a difference in patient outcomes are lacking. Participants suggested that metrics to assess the effectiveness of REMS programs be developed as part of the standardization process. Assessments could permit replication of effective REMS programs and elimination of ineffective ones. Marginal programs could be altered to more closely achieve the desired outcome.

**Proposed tiered REMS model to improve REMS communications**

Participants agreed that to implement REMS programs most effectively, providers would benefit from improved and standardized components. More structure and standardization would eliminate much of the confusion that surrounds REMS implementation. Organizing REMS into a tier-based approach was suggested in the APhA 2009 REMS white paper. This concept is similar to controlled substances, which are organized into levels known as schedules (i.e., Schedule II through V). Providers have a general idea of the requirements to prescribe and dispense a certain schedule of drug. For example, providers are knowledgeable that Schedule II is the most restrictive level and requires more administrative steps to dispense compared with drugs in Schedules III through V.

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

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

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

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

**Session summary**

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

**Discussion III: Using existing technology in the provider workspace for REMS implementation**

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

**Integrating REMS into existing technology systems in practice settings**

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

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

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

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

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

Need for improved access to REMS information

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

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

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

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

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

Session summary

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

Discussion IV: Ensuring a sustainable business model for REMS-related provider activities

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

Options for reimbursement

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

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

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

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

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

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

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

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

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

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

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

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

Session summary
To ensure that prescribers and pharmacists have the staff and ability to meet patient care and administrative needs, several compensation models and options were discussed to address participation in REMS programs. Overall, participants suggested that the task of generating compensation was challenging. Each payment option, some argued, would pay different amounts for different services. Participants noted that current state budgets would make compensation from state-run programs unlikely. Altering Medicaid also would be a challenge because the effort would require lobbying each state. In addition, some voiced strongly that manufacturers should pay for REMS activities because they are creating the products requiring REMS. Some participants were concerned that a manufacturer-driven compensation model may present conflict of interest or other issues. However, other participants said it would make sense for manufacturers to help pay for services to ensure their medications are taken safely. Participants also discussed the need for additional information and cost analysis on the overall costs and administration to implement REMS programs.
Recommendations
Navigating the regulatory landscape amid the growing complexity of medication therapies requires collaboration between federal agencies, manufacturers, and those involved across the drug delivery spectrum. REMS programs continue to evolve as a tool to mitigate risks associated with medications that otherwise may not be approved or remain on the market. High-risk/high-reward therapies can improve patient outcomes, but they also require close monitoring by providers. Careful management of risks and benefits can create an environment focused on patient care and positive outcomes.

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

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

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

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

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

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

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

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

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

Table 3. Summary of recommendations

<table>
<thead>
<tr>
<th>Standardize design and implementation</th>
<th>Work together (all stakeholders) collaboratively to improve REMS processes and limit burden on the health care system</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardize REMS programs, components, and processes</td>
</tr>
<tr>
<td></td>
<td>Contribute to efforts of FDA to standardize REMS programs based on the spectrum of risk of a medication</td>
</tr>
<tr>
<td></td>
<td>Include input from front-line providers early in REMS design and development process</td>
</tr>
<tr>
<td></td>
<td>Test logistics of REMS programs with multiple elements prior to implementation</td>
</tr>
<tr>
<td></td>
<td>Provide adequate timelines for notification of health care providers and other stakeholders of requirements in new REMS programs</td>
</tr>
</tbody>
</table>

Maximize effectiveness
- Focus on REMS effectiveness in minimizing patient risk as a primary marker of successful programs |
- Encourage flexibility as REMS programs evolve over time in response to outcomes or changing needs |
- Engage in continuous improvement of REMS programs, modifying the program to ensure maximum effectiveness in reducing patient risk

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

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

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

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

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

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

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

Abbreviation used: EHR, electronic health record; MTM, medication therapy management; REMS, risk evaluation and mitigation strategies.

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

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

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

References


Appendix 1. Food and Drug Administration activities related to REMS

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

2009 draft guidance to FDA

In September 2009, FDA issued a draft guidance, “Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications,” to provide industry with advice on how to develop drug safety strategies and REMS programs. The draft document is available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. While this document aims to help manufacturers as they develop REMS for submission to FDA, it does not address standardizing REMS to help ensure uniform implementation within and across care settings, among different providers, and across drug products. However, the goal of REMS standardization as it relates to providers is implicit in the statutory text of the Food and Drug Administration Amendments Act of 2007 (FDAAA; PL 110-85, §901, 121 Stat. §931), which requires FDA to ensure that REMS containing elements to assure safe use (ETASU) are not unduly burdensome on patient access.

Stakeholder feedback to FDA

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

Recognizing these concerns and wanting to gather more stakeholder input on REMS requirements, goals, implementation, and effectiveness, FDA reopened the comment period on the draft document and held the 2-day REMS public meeting on July 27–28, 2010. At this meeting, FDA heard from a larger group of stakeholders about strategies to streamline and standardize the REMS process. FDA officials at the meeting noted that as they have gained experience with REMS, they have learned that some of the REMS requirements in FDAAA lack clarity. They also noted that both REMS development and implementation can be challenging. FDA is currently evaluating input from the comment period and stakeholder meetings and considering options for improving REMS programs.
Long-acting opioid REMS

In February 2009, FDA proposed requiring a classwide REMS for long-acting and extended-release opioid medications. FDA held several meetings with manufacturers and stakeholders to gather input on this proposal. In 2010, FDA issued a draft long-acting opioid REMS for consideration. In July 2010, this proposed draft opioid REMS was rejected at a joint meeting of FDA’s Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. On April 19, 2011, FDA announced that it had sent postapproval REMS letters to manufacturers and marketers of long-acting and extended-release opioid medications indicating that a REMS will be required. The goal of the REMS is to reduce risk and ensure access for patients. The REMS will focus on prescriber education, the dispensing of a patient-friendly Medication Guide, and assessment of the program. FDA’s announcement is one step of an overall coordinated intergovernmental effort to address prescription drug abuse being led by the White House Office of National Drug Control Policy. Additional information on the National Prescription Drug Abuse Plan is available at www.whitehouse drugpolicy.gov/prescriptiondrugs/index.html. Additional information on FDA’s opioid REMS, the letter to manufacturers, and other resources is available at www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm.

PDUFA reauthorization activities

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

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

FDA draft guidance on MedGuides in REMS

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

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


Improving patient medication information and MedGuides

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

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

FDA non-REMS patient safety activity

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


Appendix 2. American Pharmacists Association activities related to REMS

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

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

In addition, APhA has been involved with and supports FDA’s efforts to improve MedGuides and develop a new patient medication information (PMI) document. APhA also supports FDA’s efforts to revise how MedGuides are used in REMS.
APhA 2009 REMS white paper
On July 15, 2009, APhA convened a small panel of stakeholders to explore the development and implementation of standardized solutions to REMS. Meeting participants included representatives of pharmacists, prescribers, researchers, patient advocates, and nurses, and was observed by a representative from FDA. The 2009 meeting explored experiences with existing REMS and discussed options for developing future REMS programs, with an emphasis on a systematic solution that would be feasible for the health care system. Stakeholder meeting participants engaged in open and candid discussion about their experiences and thoughts for moving forward with developing a standardized, system-based process for implementing any REMS program.

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

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

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

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

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