

Risk Evaluation and Mitigation Strategies

DISCUSSION GUIDE



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Continuing Education Discussion Guide

Executive Summary

Determining the relative safety of potentially beneficial, even life-saving pharmaceuticals without causing undue delay in their approval is an important goal of the U.S. Food and Drug Administration (FDA) and regulatory agencies worldwide. Just as paramount is monitoring emerging safety information about marketed products, in order to ensure their benefits continue to outweigh their known risks. To these ends, legislation has been enacted to provide various safeguards, including risk evaluation and mitigation strategies (REMS) in the United States, before and after product approval.

In 1999, the FDA Task Force on Risk Management reviewed the agency's medical product risk management practices within the context of the entire U.S. healthcare delivery system. The Task Force concluded that while the FDA's postmarketing surveillance and risk assessment activities were functioning as designed, improvements could be made via such steps as integration of extant systems, intensified surveillance of newly marketed products, and development of new methodologies for available safety databases.

In 2002, representatives from pharmaceutical manufacturers and regulatory authorities in the United States, European Union, and Japan proposed development of an international guideline to assist in planning pharmacovigilance activities before and after product approval to reduce the risk of drug toxicity and increase public health benefit.

After two years of work, in late 2004 the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) released its *E2E: Pharmacovigilance Planning* guideline, which FDA published as a finalized guidance in April 2005. E2E advocates pharmacovigilance planning throughout the product life cycle, beginning with preclinical studies and continuing with human clinical trials, with a safety specification to be crafted that summarizes important identified risks, potential risks, and missing information from the premarketing database. Based on this specification, a pharmacovigilance plan is then formulated to address the safety issues in preparation for the early postmarketing period. Both the safety specification and pharmacovigilance plan are to be updated as more safety information becomes available during the product's time on the market, thus continuing the life cycle approach to risk assessment and management.

Although routine pharmacovigilance (including fulfillment of mandated regulatory safety reporting, updating of labeling based on new safety information, and signal detection/evaluation) is generally sufficient as risk management for most drug products, some pharmaceuticals merit consideration for additional risk minimization efforts. With that in mind, in 2005 FDA published a new guidance, *Development and Use of Risk Minimization Action Plans* (RiskMAPs), which describes strategic safety programs designed to meet specific goals and objectives in minimizing a product's known risks, while preserving its benefits.

Executive Summary (continued)

RiskMAPs tools are classified into three categories of ascending complexity, namely (1) targeted education and outreach, (2) reminder systems, and (3) performance-linked access systems. While pharmaceutical risk management plans had been implemented in the U.S. before publication of the RiskMAP guidance (e.g., monitoring program for agranulocytosis in association with clozapine use), the document provided valuable information and guidance regarding an overall approach for such programs.

New legislation, namely the Food and Drug Administration Amendments Act of 2007 (FDAAA), further strengthened FDA's postmarketing authority with respect to drug safety, including new requirements for REMS and postmarketing studies. The goals, tools, and structures of RiskMAPs and REMS are quite similar, and both can be instituted at any time in a pharmaceutical's life cycle. However, RiskMAPs are covered in an FDA guidance, while under FDAAA the FDA has designated enforcement authority with respect to REMS, with stipulated civil monetary penalties that can be imposed for violations of REMS-related provisions.

Components of REMS may include medication guides, patient package inserts, communication plans, elements to assure safe use (ETASUs), and implementation systems, and must include a timetable for REMS assessment. Similar to performance-linked access systems under the RiskMAP guidance, ETASUs are to include one or more goals to mitigate a specific serious risk listed in the labeling of a drug, and, to mitigate such risk, may require that:

- Healthcare professionals who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or healthcare settings that dispense drug are specially certified;

- The drug is dispensed to patients only in certain healthcare settings, such as hospitals;
- The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
- Each patient using the drug is subject to certain monitoring; or
- Each patient using the drug is enrolled in a registry.

Just as with RiskMAPs and risk minimization programs predating the recent FDA initiatives, the underlying rationale for imposing a REMS is to ensure availability of a pharmaceutical that might otherwise not be approved for marketing in the U.S., or withdrawn from the American market, due to a significant risk. Although FDA seeks to minimize the burden on healthcare systems and avoid interfering with patient access to medications, REMS with ETASUs can be labor-intensive for healthcare professionals and the settings in which they deliver patient care.

The implementation and management of REMS provide opportunities for pharmacists and physicians to work with FDA and the regulated industry to improve patient safety, foster safe use of approved pharmaceuticals, and provide valuable feedback from "the trenches." Collaborative and proactive efforts by pharmacists and physicians working through professional organizations, with specialty pharmacies, and with institutional pharmacy and therapeutics committees can help to educate their fellow healthcare professionals about the management of REMS, garner valuable end-user information regarding REMS effectiveness, and provide a trusted forum for discussion of perceived burdens that such programs may engender in clinical settings.

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To best appreciate both the current status of RiskMAPs and REMS and the context for their development and implementation, a background in the origin, rationale, and evolution of FDA risk management initiatives is most helpful. Risk minimization measures long predate the release of ICH and FDA risk management documents currently in use and the FDAAA legislation passed by Congress in 2007. One example is the innovative risk minimization program in which clozapine, the first FDA-approved agent for treatment-resistant schizophrenia, could only be prescribed and dispensed through a system incorporating weekly white blood cell monitoring due to potentially life-threatening agranulocytosis.^{1,2} The program, which continues to this day in a revised form due to knowledge gained over time, was introduced in 1990.

FDA Task Force on Risk Management

In 1998, the FDA Task Force on Risk Management was established to determine whether there was a problem with the FDA drug safety program, and evaluate the agency's role in, and system for, managing risks associated with use of FDA-approved medical products (i.e., drugs, biologics and medical devices). The following year the Task Force issued a landmark report to the Commissioner after assessing medication risk management practices within the U.S. healthcare delivery system, focusing on the roles and responsibilities of each participant, and applying a risk management model used in other government sectors (e.g., the Federal Aviation Administration).³ Participants and their respective roles include

1. Manufacturers who develop and test medical products in pre-clinical studies and human clinical trials, and then submit applications for marketing approval to FDA;
2. FDA, which conducts extensive premarketing pharmaceutical review in its approval process, in tandem with ongoing postmarketing passive and active surveillance activities programs to gather new safety data for use in monitoring a product's evolving benefit/risk profile;
3. Healthcare professionals and other participants in the overall healthcare delivery system, who must select pharmaceuticals based on the latest available product labeling in order to foster safe use; and
4. Patients and other healthcare consumers, whom over the past few decades have become increasingly knowledgeable about pharmaceutical treatments and assumed more active roles in their own care.

While FDA plays a vital role in pharmaceutical risk management via its premarketing and postmarketing programs, the Task Force emphasized that FDA is only a component in the complex nationwide system of risk management, with the role of other participants less clearly defined.³

As part of its mandate, the Task Force examined whether an increase in drug market withdrawal rates or unexpected serious adverse events requiring labeling changes might have occurred after 1990 due to several legislative (e.g., 1992 enactment of the Prescription Drug and User Fee Act [PDUFA]) and managerial initiatives designed to speed Agency premarketing review. Under PDUFA, Congress authorized FDA to collect user fees from manufacturers of human drug and biological products specifically designated for use in FDA premarketing review activities, including training and hiring, to expedite availability of products appropriate for marketing approval. The Task Force found that drug marketing withdrawal rates for safety reasons remained relatively unchanged (and relatively low) over the preceding decades, despite an appreciably shortened drug review time achieved by the agency under PDUFA. Another important indicator, unexpected serious adverse events resulting in labeling changes after approval, were found to be occurring less often than in the past.³

The Task Force pinpointed several factors inherent to the drug product development process that limit ability to detect rare, serious adverse events before marketing, including the relatively small numbers of patients exposed, relatively short duration of clinical trials, and exclusion criteria that often result in patient populations involved in clinical trials that are not representative of the actual population that will be exposed once the product enters the market.^{1,4} While modifying the

drug product development process to mitigate these factors could increase the ability to identify serious risks before product marketing, such changes would increase development costs and delay product availability, according to the Task Force.³

In other major findings, the Task Force reported that FDA's predominantly passive postmarketing surveillance programs were adept at rapidly identifying most serious unexpected adverse events occurring after approval, along with increased knowledge of the severity of known risks. In concluding these programs were performing as designed for their specific goals, the Task Force emphasized they were not designed to assess the rate, or impact, of known adverse events.³

Options to enhance the agency's ability to evaluate serious adverse events by supplementing its passive systems and thus improve the effectiveness of its overall risk management activities, were presented by the Task Force. These recommendations included providing ongoing professional education and core competency training for all reviewers, integrating established postmarketing systems so that all information would be readily available to reviewers, intensifying surveillance of newly marketed products, developing new methodological tools, and meeting with stakeholders to discuss the current system for managing risks.

A key finding of the Task Force was that a systems framework should be applied to medical product risk management. Such a framework would incorporate increased understanding of the types and sources of risks associated with medical product use to enhance effectiveness of risk interventions and facilitate integration of the varied efforts of all interested parties.

Options to improve FDA risk management activities and the overall system of managing the risks from mediations also were identified by the Task Force. These included implementing mechanisms to address the limitations inherent in premarketing development or obtain postmarketing information (e.g., prospective product use registries), augmenting FDA epidemiologic and methodologic research activities and the agency's role and responsibilities in risk communication, and seeking legislative changes for risk intervention (e.g., suspension authority for drugs).³

International Initiative

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a collaboration of pharmaceutical manufacturers and drug regulatory authorities in Europe (i.e., the European Union), Japan, and the United States was established in 1990.⁵ The goal of ICH is standardization of regulatory requirements, with its expert working groups generating guidelines containing recommendations on how to achieve greater harmonization in both interpretation and application of such standards. These guidelines are crafted through a rigorous evaluation and review process but carry no formal regulatory weight, as they must be incorporated into national regulations or other appropriate measures (e.g., issuance of guidances in the U.S., which are published in the *Federal Register*).

Achieving international regulatory harmonization is beneficial to regulatory authorities, pharmaceutical industry, and protection of public health. By preventing duplication of clinical trials in humans and minimizing use of animal testing without compromising safety and effectiveness, streamlining the regulatory assessment process for new drug applications, and reducing development times and resources for drug development, pharmaceuticals with demonstrated benefits can emerge onto markets in less time.⁵

In 2001, pharmacovigilance, defined as the scientific activities relating to the detection, assessment, understanding, and prevention of adverse effects or other drug-related problems, including pharmacoepidemiologic studies, was a major topic of ICH discussion. The following year, a proposal for development of an international guideline to assist the pharmaceutical industry and regulatory agencies in planning pharmacovigilance activities, especially in the early post-marketing period for new drugs, was endorsed.⁶

The underlying rationale for the final concept paper, *E2E Pharmacovigilance Planning*, is that carefully planned and effective pharmacovigilance activities, particularly for new drugs, can reduce risk of drug toxicity and increase public health benefit; in addition, robust safety data can help avoid effective drugs coming off market.

The E2E: Pharmacovigilance Planning Guidance

In November 2004, the resulting ICH guideline, *E2E: Pharmacovigilance Planning*,⁷ was released and was published as a finalized guidance in the U.S. in April 2005.⁸ FDA guidance documents represent the Agency's current thinking on a particular subject, but unlike regulations or statutes, are not enforceable per se. However, the approach described in an FDA guidance can be used if it satisfies requirements of the applicable statute and regulations; an alternative approach needs to be discussed with FDA staff responsible for the guidance.⁹

E2E describes a process for planning pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug or biological product, throughout the entire product lifecycle, starting with non-human preclinical testing.⁸ Taking a science-based approach to risk documentation, a safety specification is crafted from data generated in the entire premarketing program, along with an associated pharmacovigilance plan. In addition, the guidance outlines principles of good practice for the design and conduct of observational studies that may provide further important safety information in the premarketing and postmarketing periods.

The safety specification is a method for summarizing identified risks, potential risks, and missing information that includes potentially at-risk populations and situations in which the pharmaceutical is likely to be used in medical practice, but was not studied before approval. Identified risks can arise from both preclinical testing (such as safety issues not adequately addressed by the available clinical data) and clinical trials (limitations of the human safety database, such as study population size, inclusion/exclusion criteria or populations not studied, such as pediatric and geriatric patients, and patients with relevant co-morbidity should be considered) along with any worldwide experience with the product. The epidemiology of the disease state being treated should be discussed, along with detailed adverse event/adverse reaction information, including identified and potential drug-drug and drug-food interactions based on the clinical pharmacology of the product.

The guidance is most useful for new chemical entities, biotechnology-derived products, and vaccines, as well as for substantial changes in established products (e.g., new dosage forms, routes of administration, or manufacturing processes for biotechnology-derived products) and for established products that will be introduced to a new patient population, have an important new indication, or when new major safety concerns arise.

The underlying paradigm is that a pharmaceutical's benefit/risk profile needs to be closely monitored throughout its lifecycle and that additional risk minimization measures beyond routine pharmacovigilance may be necessary to address significant safety concerns. As dynamic documents, both the safety specification and pharmacovigilance plan should be revised as more information about the product's safety becomes available and milestones are reached in postmarketing experience.⁸

As noted, the E2E guidance is not incorporated into FDA regulations, so there is no requirement for either a safety specification or a pharmacovigilance plan to be submitted with each new pharmaceutical licensing application in the U.S. That is not the case in the EU, as the then EMEA's "Guideline on Risk Management Systems for Medicinal Products for Human Use"¹⁰ went into effect in November 2005 with an EU Risk Management Plan (EU-RMP) that used E2E concepts and language. The circumstances for which an EU-RMP is required are consistent with E2E and consist of the following two parts:

1. **Part I:** Safety Specification and Pharmacovigilance Plan (as in E2E), with additional EU requirements as to potentials for overdose, transmission of infectious agents, and misuse for illegal purposes in the Safety Specification.
2. **Part II:** Evaluation of need for risk minimization activities—if there is need for additional (i.e., non-routine) risk minimization activities, RMP also includes risk minimization plan.

As will be seen, the European Guideline's *Annex B: Methods for Risk Minimization*¹⁰ has elements in common with an important FDA risk minimization guidance released in its final version the same year.

Risk Minimization Action Plans (RiskMAPs)

In March 2005, as part of its pharmaceutical risk management initiative, FDA published three final risk minimization guidances, *Premarketing Risk Assessment*, *Development and Use of Risk Minimization Action Plans (RiskMAPs)*, and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.¹¹

In the RiskMAP guidance, this special plan is defined as a strategic safety program designed to minimize known risks of a product while preserving its benefits.¹² Indicative of the linkage between ICH and FDA initiatives, per the RiskMAP guidance, such a program could be considered a selectively used type of safety action plan as defined in E2E guidance.

Regarding RiskMAPs, routine risk minimization measures, such as periodic updating of FDA-approved professional labeling to incorporate information derived from postmarketing surveillance or studies revealing new benefits or risk concerns, along with good reporting practices, were thought by FDA to be sufficient for most products (i.e., no RiskMAP).

When a significant risk warrants the establishment of a RiskMAP, it might be identified before or after product marketing.¹² At a 2007 public workshop on RiskMAP implementation, FDA reported that as of February 2007, approximately 30 drugs had RiskMAPs in place. Nine of these plans were developed after the drug was marketed.

The decision to implement a RiskMAP is made on a case-by-case basis, taking into consideration the following critical clinical factors:

- Nature and rate of known risks compared with benefits, including the types, magnitude, and frequency of risks and benefits;
- Populations at greatest risk and/or likely to derive the most benefit;
- Availability of treatment alternatives and associated risks and benefits; and
- Preventability and reversibility of adverse events observed.

When a RiskMAP is deemed necessary, there are three general categories of tools that are to be utilized in service of specific, clinically relevant goals:

(1) targeted education and outreach, (2) reminder systems, and (3) performance-linked access systems.¹²

Specific targeted education and outreach efforts are used to increase appropriate knowledge of key people or groups (e.g., health professionals and consumers) with the capacity to prevent or mitigate product risks of concern. When targeted education and outreach tools are deemed insufficient to minimize risks, reminder systems may be used to prompt, remind, double-check, or otherwise guide healthcare professionals and/or patients in prescribing, dispensing, or receiving the pharmaceutical in ways that minimize risk.

Performance-linked access systems are recommended for products that have significant or otherwise unique benefits in a particular patient group or condition, but also carry unusual risks, such as irreversible disability or death, and routine risk minimization measures, targeted education and outreach tools, and reminder systems are either known or likely to be insufficient to minimize those risks.¹²

Both reminder systems and performance-linked access systems are proactive risk management tools, and performance-linked access systems can be particularly burdensome. As of February 2007, all of the approximately 30 RiskMAPs had targeted education and outreach as a component, with 10 including performance-linked access or reminder systems.

Food and Drug Administration Amendments Act of 2007

National and international risk mitigation initiatives notwithstanding, an impetus for Congressional action was a 2006 Institute of Medicine report on drug safety, which offered recommendations including the following:

- Labeling requirements and advertising limits for new medications,
- Clarified authority and additional enforcement tools for FDA,
- Clarification of agency's role in gathering and communicating additional information on marketed products' risks and benefits,
- Mandatory registration of clinical trial results to facilitate public access to drug safety information,
- Increased role for FDA's drug safety staff, and
- Large boost in funding and staffing for FDA.¹³

Possible imposition of REMS was not without controversy. FDA noted in testimony before Congress that RiskMAPs were already being utilized by the Agency and industry for products warranting additional risk minimization measures and that FDA already had authority to mandate post-approval studies in specific circumstances.¹⁴ FDA's then Deputy Commissioner for Policy concluded:

"Improved drug safety is not simply a matter of extending new legal authorities to FDA or requiring the Agency to engage in certain detailed activity. Indeed, extending these interventions or expanding the use of REMS is unlikely to result in improvements in drug safety as desired by the bill's sponsors."¹⁴

The Food and Drug Administration Amendments Act (FDAAA) was signed into law on September 27, 2007. It amended the Federal Food, Drug, & Cosmetic Act and reauthorized PDUFA.¹⁵

REMS

Title IX of FDAAA enhances FDA's postmarketing authorities with respect to drug safety, with section 901 granting FDA new authorities to require post-marketing studies or clinical trials of human drugs and REMS.¹⁵ While both REMS and RiskMAPs are similar in structure, rationale, tools, goals, scientific rationale, and public health intent, there are important regulatory differences. RiskMAPs remain in effect for those pharmaceuticals for which risk management programs do not meet REMS criteria. RiskMAPs are guidance-specified, as opposed to being covered by a rule, law or regulation. In contrast, REMS are a FDAAA provision.^{12,15,16} REMS, unlike RiskMAPs, are not an FDA construct, but rather a Congressional mandate for which FDA is responsible under FDAAA. REMS are enforceable by FDA and subject to inspection, with specified penalties for non-compliance. While the RiskMAP guidance specifies the need for ongoing assessment and revision of such programs, it does not present a specified timetable for submission of assessments, such as that for REMS under FDAAA.¹²

In FDA's first notice issued under its new drug safety authorities under FDAAA, it identified 16 drugs and biologics approved/licensed before FDAAA provisions took effect on March 25, 2008, deemed to have REMS.¹⁷

All had RiskMAPs in place before that determination, and holders of applications deemed to have in effect an approved REMS were required to submit a proposed REMS to FDA.¹⁷

In an effort to assist the pharmaceutical industry in crafting REMS, FDA released a draft guidance, *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, in September 2009.¹⁶ With respect to the relationship between RiskMAPs and REMS, FDA stated that many principles included in its RiskMAP guidance are embodied in FDAAA REMS provisions as implemented by the agency. FDA further stated that the RiskMAP guidance continues to apply to products with existing RiskMAPs (e.g., products with RiskMAPs not deemed to have an approved REMS in effect) and to products with new RiskMAPs (e.g., abbreviated new drug approvals [ANDAs] for which the reference listed drug has a RiskMAP).¹⁶

The major regulatory similarities between RiskMAPs and REMS, include the following:

- Neither is required for most products,
- Neither is required to be submitted with each new drug application (NDA) biologics license application (BLA) or ANDA,
- Both are judged necessary by FDA to ensure that a drug's benefits outweigh its risks,
- Requirement for either can emerge during premarketing or postmarketing evaluation.

On a clinical/scientific basis, there are major similarities between RiskMAPs and REMS, including the threshold of patient harm that needs to be reached for such a program to be deemed necessary by FDA to ensure that a drug's benefits outweigh its risks. Following are factors that are assessed in making such a determination:

- Estimated size of population likely to use drug,
- Seriousness of disease or condition to be treated,
- Expected benefits of drug with respect to disease or condition,
- Expected or actual duration of treatment, and
- Seriousness of any known or potential adverse events.^{12,15}

With respect to a drug's health professional labeling, the ICH E2E guideline, FDA RiskMAP guidance, and FDA REMS draft guidance all emphasize the importance of its periodic updating to incorporate information from postmarketing surveillance or studies revealing new benefits or risk concerns.^{8,12,16} As with RiskMAPs, a product's labeling may drive a need for REMS, as a boxed warning may already exist or be deemed necessary based on new safety information and/or re-evaluation of previous data.

While perhaps not as clearly delineated as in the RiskMAP guidance, there is a hierarchy to the tools to be employed in REMS in an effort to achieve specific risk mitigation goals resulting in desired safety-related health outcomes. Similar to RiskMAPs, REMS risk management tools can include a medication guide, patient package insert, communication plan, and/or elements to assure safe use (ETASUs).¹⁵

As one element of a REMS, FDA may require that a medication guide be developed per 21 CFR 208, which specifies requirements for patient labeling for those human prescription drugs, including biologics, that FDA determines pose a serious and significant public health concern that necessitates distribution of FDA-approved patient information. Medication guides usually do not involve participation of a learned intermediary (i.e., product is used by consumers on an outpatient basis without direct healthcare professional supervision). Table 1 lists circumstances in which a medication guide is required.

A communication plan for healthcare providers may be part of a proposed REMS. Sending letters about serious risks from drugs and REMS requirements directly to healthcare providers or communicating such information through professional organizations (e.g., member news briefs) may be part of the communication plan.^{15,16} There is a considerable literature on notifications,¹⁸ including work performed by FDA's MedWatch program in safety-related notification to healthcare professionals and consumers through its MedWatch partners program.

Per FDAAA, ETASUs may be required to provide safe access for patients to drugs with known serious risks that would otherwise be unavailable, if FDA determined (1) that drug, which has been shown to be effective

TABLE 1.
**Situations in Which a
Medication Guide is Required
by FDA as Part of REMS^{15,16}**

1. The drug product is one for which patient labeling could help prevent serious adverse effects.
2. The drug product is one that has serious risks (relative to benefits) about which patients should be made aware because information concerning the risks could affect the patient's decision to use, or continue to use, the product.
3. The drug product is important to health and patient adherence to directions for use is crucial to effectiveness.

FDA = Food and Drug Administration

REMS = risk evaluation and mitigation strategies

A medication guide is required in any of the above circumstances.

but associated with a serious ADE, can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate specific serious risk listed in labeling of drug, and (2) that for drug initially approved without ETASUs, other possible elements of REMS are found to be insufficient for mitigating serious risks.¹⁵

ETASUs are to include one or more goals to mitigate specific serious risk listed in the drug's labeling. To mitigate such risk, ETASUs may require that

- Healthcare professionals who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified;
- Drug is dispensed to patients only in certain health care settings, such as hospitals;
- Drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;

- Each patient using drug is subject to certain monitoring; or
- Each patient using drug is enrolled in a registry.

Such interventions are consistent with performance-linked access systems as detailed in the RiskMAP guidance.¹²

FDA may require an implementation system for REMS that includes ETASUs. Through such a system, the applicant (sponsor company) may be expected to monitor and evaluate REMS implementation by responsible healthcare professionals, and work to improve their implementation.^{15,16}

The FDA may require the implementation system to address the distribution and dispensing of drug products to ensure that REMS requirements are met (i.e., drugs are distributed by wholesalers only to certified or otherwise specified pharmacies, practitioners, or healthcare settings dispensing drug, or only to patients meeting REMS requirements). Other examples of methods used by applicants to monitor and evaluate implementation of REMS with ETASUs include the following:

- Maintaining a validated and secure database of all certified entities (pharmacies, practitioners, and healthcare settings) to ensure any certification requirements or other requirements are met,
- Conducting periodic audits of pharmacies, practitioners, and healthcare settings to evaluate compliance with ETASUs (e.g., documentation of safe-use conditions prior to dispensing drug), and
- Conducting periodic audits of wholesale shipment or distribution systems to determine drug is only being distributed to authorized entities for ETASUs that include on where and how a drug may be dispensed.

Both RiskMAP tools and REMS elements to ensure safe use are designed to help achieve one or more specific objective as part of overall goal, and the varied sources of "New Safety Information," including clinical trials, adverse event reports, postapproval studies, and other scientific data deemed appropriate regarding serious risks or unexpected serious risks associated with use of drug, are identical for both RiskMAPs and REMS.^{12,15,16} As with RiskMAPs, FDA may require REMS post-approval if new safety information suggests that such

strategies are needed to ensure that the benefits of the drug outweigh its risks.

A REMS goal is defined as "The desired safety-related health outcome or the understanding of serious risks targeted by the use of specified REMS elements," and should be stated in such a way as to achieve maximum risk reduction.^{15,16} Goals should be stated in absolute terms. While it might not be possible to ensure a goal can be met for every patient, FDA considers a goal is to be a statement of a REMS's ideal outcome.¹⁶ As such, REMS goals should be associated with pragmatic, specific, and measurable program objectives and that as with RiskMAPs, continuous assessment and modification of REMS are required to ensure that the strategies used remain effective for minimizing the serious risks associated with drugs.

Following is the required timetable for submission of REMS assessments:

- By 18 months and 3 years after the strategy is initially approved,
- In the seventh year after the strategy is approved, or
- At another frequency specified in the strategy.¹⁵

Additional deadlines for submission may be established if more frequent assessments are needed to ensure that the benefits of the drug continue to outweigh its risks. The 7-year assessment may be eliminated if FDA determines after the initial 3-year period that serious risks of the drug have been adequately identified and assessed and are being adequately managed.

As a Congressional mandate, REMS requirements are subject to inspection and enforceable, with monetary penalties for violations.¹⁵ The penalties imposed on manufacturers for violation of REMS requirements may be substantial, amounting to as much as \$250,000 per violation and \$1 million for all violations adjudicated in a single proceeding. If a violation continues after the manufacturer receives written notice, a penalty of up to \$10 million may be imposed for all violations in a single proceeding. In determining the amount of the penalty, the agency takes into consideration whether the manufacturer is making efforts to correct the violation.

A significant difference between REMS and RiskMAPs has proven to be one of the most problematic, namely

those programs that use a medication guide without any other risk mitigation measures. FDA has been considering every new medication guide (or those revised for safety-related changes) to be part of a REMS,¹⁶ which is not the case with RiskMAPs. An examination of REMS approved by FDA since FDAAA went into effect demonstrates this fact. As of April 6, 2011, of 176 approved REMS for distinct active moieties, 113 involved solely a medication guide, while another 40 involved only a medication guide and communication plan (87% of total approved REMS).¹⁹

FDA, in recognizing healthcare professional and industry concerns about medication guides, including distribution in outpatient versus inpatient settings, has issued a draft guidance entitled *Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*²⁰ and an associated questions and answers document.²¹ The questions and answers document addresses this policy change, stating “that it is no longer necessary or appropriate to consider every medication guide to be an element of a REMS.”²¹

Drug sponsors have been instructed that implementation of the new policy on Medication Guide-only REMS will be accomplished by allowing them to request removal of a REMS when the only element is a medication guide and timetable for assessment; this process is also explained in the questions and answers document.²¹ If the REMS is indeed removed, the drug will still have a medication guide requiring distribution according to FDA regulations and circumstances outlined in the draft guidance.^{20,21}

Opportunities and Issues in REMS Implementation and Management

The safeguards provided by REMS allow drugs with known serious adverse effects to be approved for marketing in the first place or to remain on the market and available to patients who stand to benefit from them. At the same time, implementing and managing REMS, particularly those that require ETASUs, can place a burden on healthcare practitioners because of the lack of standardization and time-consuming nature of the requirements. The perceived advantages and disadvantages of REMS are outlined in Table 2.

In considering these positives and negatives, certain factors should be kept in mind. As REMS requirements

TABLE 2.
**Advantages and Disadvantages
of REMS Requirements**

Advantages

- Promote safe and appropriate use of drugs
- Provide opportunities for systematic data collection, reporting, and feedback on medication safety
- Allow drugs to be approved that would not otherwise have been approved because of risks
- Allow drugs that might have been withdrawn from the market because of risks to remain on the market
- Provide opportunities for expanded clinical and leadership roles and collaboration among pharmacists, physicians, and other healthcare practitioners

Disadvantages

- Lack of standardization
- Potential for confusion among healthcare practitioners
- Time-consuming, labor-intensive nature
- Lack of reimbursement for extra work involved
- Insufficient healthcare practitioner input to FDA in premarketing development of REMS
- Potential for disruption in continuity of patient care

FDA = Food and Drug Administration;

REMS = risk evaluation and mitigation strategies

are relatively new, there is a steep learning curve for all involved parties. Those involved in REMS implementation and management (e.g., FDA, sponsors, healthcare professionals, healthcare institutions) are gaining experience in how best to perform these critical functions, and it is reasonable to expect this will lead to more effective (and hopefully, less time-consuming) REMS-related activities over time. Toward that end, in July 2010 FDA held a two-day public meeting to obtain stakeholder

views on REMS, concentrating on issues and challenges posed by their development and implementation²².

Few REMS involve ETASUs. Of all REMS approved by FDA since FDAAA went into effect, only 22 (13%) include an ETASU.¹⁹ FDA has begun to address medication guide-related issues, including REMS classification and distribution in the inpatient and outpatient settings.

Congress and FDA manifest concern about possible burdens caused by REMS, including patient access to drugs with REMS as well as on healthcare delivery systems. FDAAA includes a provision for FDA to seek input from patients, physicians, pharmacists, and other healthcare providers about how ETASUs may be standardized to avoid being “unduly burdensome” on patient drug access and, to a practicable extent, minimize burden on the healthcare delivery system.¹⁵ FDA’s next steps for REMS include the development of a framework for their improvement, including public outreach. FDA has stated its objective is to “develop standardized REMS that can be plugged into existing healthcare systems to address particular risks and categories of risk.”²²

Concerning input from healthcare professionals, there are clear differences between REMS undergoing development for drugs not yet approved versus drugs that are already on the market. Pharmacists, physicians, other healthcare professionals, and their professional organizations may be approached by a sponsor for feedback about elements of REMS; however, the proprietary nature of premarketing data precludes open discussion until the approval process is complete.

Conversely, for marketed products, there is much greater transparency and availability of information. The experience of healthcare professionals with such products would be an important resource in developing REMS. Although healthcare specialty organizations are a logical resource for providing input to FDA, the pharmaceutical sponsors are responsible for designing, implementing, and managing REMS. Physicians, pharmacists, and other healthcare professionals should be encouraged to provide feedback to the company holding marketing authorization.

Physicians and pharmacists should take a leadership role in their institutions with regard to managing drug products REMS requirements, particularly those with ETASUs. Pharmacy and therapeutics (P&T) committees are in a unique position to address REMS requirements through a collaborative process and gather valuable data regarding their management and impact on patient care. The P&T committee is the logical institutional organization for development of policies, procedures, and forms for the use of drugs with REMS.

The implications of ETASUs and other REMS requirements for every step in the medication-use process (i.e., prescribing, dispensing, administration, and monitoring) should be taken into consideration when developing policies and procedures. The use of integrated healthcare delivery systems with electronic health records that tie together medication orders, medication administration records, laboratory data, and other patient information across the healthcare continuum (i.e., hospital, office practice, home) offers a promising avenue for enhanced compliance with REMS requirements and generation of useful clinical data for improving REMS in specific and in general.

Conclusion

FDA and regulatory authorities in other countries seek to avoid market withdrawal, or non-approval of drugs with known serious risks without unduly interfering with patient access to the benefits of these drugs. Use of REMS facilitates these goals, but ETASU requirements in particular can be burdensome to healthcare professionals and healthcare delivery systems. Pharmacists and physicians need to be aware of the background and current status of regulatory risk minimization initiatives and work collaboratively with their fellow healthcare professionals, healthcare institutions, specialty organizations, consumer groups, national medical product regulatory agency, and pharmaceutical industry to enhance REMS effectiveness and improve medication safe use.

Target Audience

This activity was planned to meet the needs of physicians and pharmacists practicing in large and small health systems, as well as in ambulatory care, managed care, home care, long-term care, and academic settings. This activity would be particularly beneficial for physicians, pharmacists, clinical specialists, managers, decision makers, and educators who are interested in current regulatory considerations related to ensuring the safety of medications.

Learning Objectives

After participating in this knowledge-based activity, participants should be able to

1. Describe the goals, origins, and evolution over the past decade of medication safety initiatives by the Food and Drug Administration (FDA) and worldwide regulatory agencies.
2. Discuss the FDA guidance on E2E pharmacovigilance planning, and identify and characterize its key parts.
3. Compare and contrast the goals, requirements, terminology, and legal enforceability of risk minimization action plans (RiskMAPs) and risk evaluation and mitigation strategies (REMS).
4. Identify an issue associated with implementing and managing REMS in health systems and suggest a suitable approach to address the issue.

Accreditation for Pharmacists



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.5 hours (.15 CEUs) of continuing pharmacy education credit (ACPE activity #204-000-11-408-H05P).

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The American Society of Health-System Pharmacists designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credit(s)*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

To receive continuing education credit, participants must read this guide, and visit the ASHP CE Center to take the activity post-test for **pharmacists** or **physicians** and complete the evaluation. A minimum score of 70% is required on the test for credit to be awarded, and participants may print their official statements of continuing education credit immediately. This activity is provided free of charge and is available from May 31, 2011 through May 30, 2012.

This activity is sponsored by the American Society of Health-System Pharmacists (ASHP) and planned by ASHP Advantage, a division of the American Society of Health-System Pharmacists.

Post Test

For reference only. Users must visit the ASHP CE Center to take the activity post test.

1. **A primary goal of risk evaluation and mitigation strategies (REMS) and other medication safety initiatives by the Food and Drug Administration (FDA) is**
 - a. To prevent the use of drug products with known serious risks.
 - b. To avoid market withdrawal of drug products with known serious risks.
 - c. To promptly remove from the market drug products with previously undetected serious risks.
 - d. To delay marketing of drug products with known serious risks.
2. **Which of the following statements best reflects the conclusion of the FDA Task Force on Risk Management regarding the FDA medication safety program in its 1999 report to the FDA Commissioner?**
 - a. A complete overhaul of the program was needed to correct major deficiencies.
 - b. Improvements were needed to correct shortcomings of the medication safety program, which was not functioning as designed.
 - c. Improvements to build on the program, which was functioning as designed.
 - d. No changes were needed in the program, which was functioning as designed.
3. **Which of the following are key parts of the FDA guidance on E2E pharmacovigilance planning?**
 - a. Targeted education/outreach and reminder systems.
 - b. A medication guide/patient package insert and elements to assure safe use (ETASUs).
 - c. A communication plan and implementation system.
 - d. A safety specification and pharmacovigilance plan.
4. **Which of the following could be considered a selectively used type of safety action plan as defined in the guidance on E2E pharmacovigilance planning?**
 - a. Communication plan.
 - b. Risk minimization action plan (RiskMAP).
 - c. Safety specification.
 - d. Medication guide.
5. **Which of the following RiskMAP tools is proactive and usually particularly burdensome?**
 - a. Targeted education and outreach.
 - b. Reminder systems.
 - c. Performance-linked access systems.
 - d. Safety specifications.
6. **REMS and RiskMAPs differ in their**
 - a. Legal enforceability and noncompliance penalties.
 - b. Scientific rationale and risk management tools.
 - c. Goals and risk management tools.
 - d. Goals and legal enforceability.
7. **Which of the following factors is taken into consideration by FDA in determining whether a REMS is required?**
 - a. The duration of the disease or condition for which the drug will be used.
 - b. The age of the population likely to use the drug.
 - c. The size of the population studied in preclinical drug trials.
 - d. Whether the drug is a new molecular entity.
8. **Which of the following statements about requirements for medication guides for drugs with REMS is correct?**
 - a. Medication guides are required when patient adherence to directions for use is crucial to effectiveness.
 - b. Medication guides are required for all drug products with REMS.
 - c. Medication guides are not considered part of the FDA-approved drug labeling.
 - d. Medication guides are not required when drug products are used on an outpatient basis.

9. Which of the following is a possible ETASU for a drug with known serious risks?

- a. Special laboratory monitoring.
- b. Medication guides.
- c. Patient package inserts.
- d. News briefs from professional organizations.

10. Which of the following schedules would comply with the timetable for submission of REMS assessments?

- a. 18 days, 3 months, and 7 months after approval.
- b. 3 months, 7 months, and 18 months after approval.
- c. 18 months, 3 years, and 7 years after approval.
- d. 3 years, 7 years, and 18 years after approval.

11. Which of the following is the most appropriate avenue for pharmacists and physicians to express concerns about patient safety and provide input related to the use of drug products with REMS and ETASUs?

- a. The Joint Commission.
- b. Their institution's pharmacy and therapeutics committee.
- c. FDA.
- d. Specialty pharmacy or other specialty supplier that provides the drug.

Appendix

Additional Web-based Resources on REMS

ASHP REMS Resource Center and Database

www.ashp.org/REMS

ASHP Answers to Frequently-Asked Questions on Medication Guides

www.ashp.org/DocLibrary/MemberCenter/SPPM/Medication-Guides-FAQ.aspx

FDA Questions and Answers on the Federal Register Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies

www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095439.htm

FDA List of Drugs with Medication Guides

www.fda.gov/Drugs/DrugSafety/ucm085729.htm

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