



### Practical Implementation of Risk Evaluation And Mitigation Strategies in Health Systems: The Experts Answer Your Questions

Questions about the risk evaluation and mitigation strategies (REMS) required by the Food and Drug Administration Amendments Act (FDAAA) of 2007 were discussed in a live webinar conducted on January 19, 2010, to follow up a Midday Symposium on the topic held at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, on December 7, 2009. An e-Newsletter released in Winter 2010 ([www.ashpadvantage.com/fdaaa/fdaaa-winter-newsletter.pdf](http://www.ashpadvantage.com/fdaaa/fdaaa-winter-newsletter.pdf)), summarizes the responses from the faculty to questions submitted by attendees at the Midday Symposium about terminology and the legal and regulatory aspects of REMS. Responses to other questions about the practical implementation of REMS in health systems are summarized in this e-Newsletter.

The purpose of REMS is to ensure that the benefits of a drug or drug class outweigh the risks.<sup>1</sup> These strategies may include medication guides, communication plans for health care professionals, and elements to assure safe use (ETASU), such as special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and use of patient registries.

Risk minimization action plans (RiskMAPs) designed to minimize risk associated with a product were required by the Food and Drug Administration (FDA) prior to enactment of the FDAAA.<sup>2</sup> Some drugs that were the focus of RiskMAPs were "grandfathered" to become the subject of REMS. Pharmacists who were familiar with RiskMAPs may be confused by the REMS terminology. Although REMS and RiskMAPs have some similarities, such as prescriber registration and patient enrollment requirements for certain drugs, REMS differ from RiskMAPs in three important ways (Table 1).

**Table 1. Key Differences between REMS and RiskMAPs<sup>3,4</sup>**

Characteristic	REMS	RiskMAPs
Time when established with respect to product approval by FDA	Before or after approval	At the time of approval
Assessment required to ensure goal of improving drug safety	Yes	No
Financial penalty for violation	Yes	No

FDA = Food and Drug Administration; REMS = risk evaluation and mitigation strategies; RiskMAPs = risk minimization action plans

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First, REMS requirements may be established for a drug before or after marketing. By contrast, RiskMAPs were established as part of the drug approval process; there was no provision to establish RiskMAPs after product approval if safety concerns arose.

Second, the FDAAA requirements for REMS include assessments 18 months, 3 years, and 7 years after the strategy is initially approved to ensure that the goal of improving drug safety is met.<sup>3</sup> RiskMAPs had no provisions for periodic assessment.

Third, the FDAAA authorized FDA to impose on manufacturers monetary penalties for violating REMS requirements.<sup>4</sup> RiskMAPs lacked such enforcement capability.

Health-system pharmacist involvement in fulfilling REMS requirements varies. In some institutions, pharmacist involvement in REMS is limited to dispensing of medication guides. In other institutions, provision of ETASU, participation in restricted drug distribution systems, or both as well as medication guide dispensing are among the responsibilities of pharmacists.

“ There are many similarities between REMS and RiskMAPs, but they aren't the same thing. ”

—Justine Coffey, J.D., LL.M.

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## Outpatient Pharmacy Management of Drugs with Complex REMS Requirements

Managing outpatient therapy involving a drug with complex REMS requirements can be difficult for pharmacists because of the time-consuming nature of REMS requirements (especially documentation) and limited availability of time and other resources. The key to success is to properly allocate limited resources to the clinical and administrative processes needed to meet REMS requirements. These processes include educating health care providers about REMS requirements, formulary decision making involving drugs and drug classes with REMS requirements, and developing policies and procedures for drugs with REMS requirements. REMS requirements should be considered in the processes for evaluating drugs for addition to the formulary and developing policies and procedures for use of the drug in the institution. The patient monitoring and reporting and access to patient medical records involved in meeting REMS requirements facilitates pharmacist efforts to enhance drug safety and promote patient adherence to drug therapy.

“ Efforts to meet REMS requirements by health-system pharmacists can enhance drug safety and promote patient adherence to drug therapy. ”

—JoAnn Stubbings, R.Ph., MCHA

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## Managing Complex REMS

The requirements associated with complex REMS can be time consuming and burdensome for health-system pharmacists. Restricted drug distribution systems are a complex REMS requirement for some drugs. For example, REMS requirements for lenalidomide, a thalidomide analog with the potential to cause human birth defects and other toxicities, include registration of prescribers and pharmacists, controlled distribution through contracted pharmacies, and signed patient-physician agreements.<sup>5</sup> The recordkeeping required and paperwork involved are onerous.

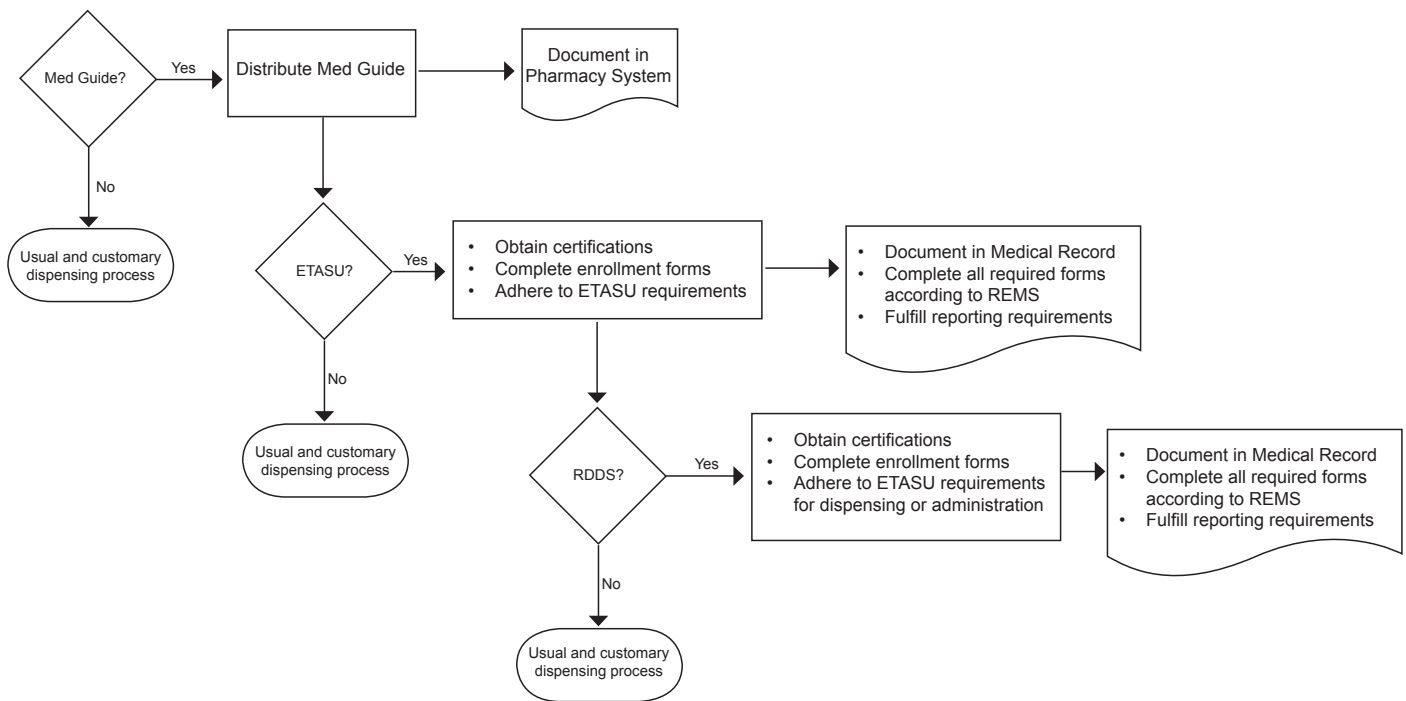
Incorporating REMS requirements into institutional policies and procedures involves consideration of general issues and specific drugs and drug classes. Table 2 is a checklist of elements to address in the process. Documentation is the most important element to address.

**Table 2. Checklist of Elements to Address in Incorporating REMS Requirements into Institutional Policies and Procedures**

- Distribution of medication guides
- Patient enrollment, laboratory testing, and monitoring
- Communications and reporting
- Provider certification
- Dispensing and administration
- Documentation

The complexity of REMS requirements, lack of a standardized approach to fulfilling these requirements, considerations in making decisions about how best to allocate limited resources to meet complex REMS requirements, and integration of processes involved in fulfilling REMS requirements into existing systems are among the issues faced by health-system pharmacists. A standardized approach to meeting REMS requirements is needed. Figure 1 shows a simplified schematic of the REMS process that may be useful in making decisions about resource allocation. Documentation is an important step throughout this flow diagram. Forms developed by manufacturers to meet REMS requirements often are substantially different from forms needed for institutional purposes.

**Figure 1. REMS Process Flow**



REMS = risk evaluation and mitigation strategies;  
 ETASU = elements to assure safe use; RDDS = restricted drug distribution systems

## FDA Flexibility

FDA is working with manufacturers to develop class-wide REMS for erythropoiesis-stimulating agents (ESAs). Dispensing of a medication guide for ESAs to the patient or caregiver currently is required by FDA. The FDA does not require dispensing of the medication guide every time the drug is dispensed because the agency recognizes that ESAs usually are administered to patients by a health care provider in a physician's office, clinic, hospital inpatient setting, or dialysis center.<sup>6</sup> A medication guide may be dispensed to such patients or a caregiver at the time of initiation of therapy and monthly thereafter, unless the medication guide is materially revised or updated. This flexible approach by FDA promotes the safe use of ESAs without imposing an undue burden on health care providers or patients.

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## Impact of REMS on Health-System Pharmacy Practice and Drug Safety

Pharmacists are ideally suited to spearhead the implementation of REMS requirements in health systems because of their education, training, and experience. Although the documentation requirements of REMS may seem burdensome, they also present an opportunity for pharmacists to assume responsibility for coordinating REMS requirements in their institutions as part of patient safety initiatives that have a favorable impact on pharmacy practice and patient outcomes.

Ideally, fulfilling REMS requirements improves drug safety and patient outcomes. REMS plans submitted to FDA by manufacturers should outline a mechanism to assess whether REMS improve drug safety.<sup>7</sup> This requirement may provide health-system pharmacists with an opportunity and the impetus to conduct research about safety outcomes from drug therapy. Comparing safety measures before and after the implementation of REMS may provide data to document a favorable impact of pharmacist efforts to meet REMS requirements. Evaluating outcome measures that reflect safety is preferred to an assessment of process measures.

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## The Future

In the future, REMS requirements will be a continuing cause for concern and controversy among health care providers and manufacturers, requiring communication among FDA, manufacturers, and others. James M. Hoffman, Pharm.D., M.S., BCPS, speculated that manufacturers may use REMS requirements as tools in negotiating with FDA to secure product approval by assuaging agency concerns about safety.

The FDAAA requires FDA to seek input from pharmacists on how REMS may be standardized so that the requirements are not unduly burdensome for the health care delivery system and do not impede patient access to potentially beneficial drug therapies.<sup>3</sup> FDA will continue to seek input about REMS from pharmacists and other stakeholders, and REMS requirements will continue to evolve and mature. Whether pharmacists are prepared to handle the growing REMS requirements remains to be seen. Pharmacist involvement in the REMS development process by providing comments to FDA will be critical in shaping REMS requirements that are workable for patients and health systems while ensuring that the goal of REMS to ensure that the benefits of a drug outweigh the risks is achieved. Dr. Hoffman views REMS as empowering for pharmacists in efforts to improve drug safety and a call to action to become involved in shaping future REMS at the patient, health system, and policy levels.

“ As drug experts, pharmacists are uniquely positioned to manage REMS requirements in health systems. ”

James M. Hoffman, Pharm.D., M.S., BCPS

## Still Have Questions about REMS?

If you would like to learn more about REMS, a web-based activity based on the live symposium is available. The web-based activity can be assessed from the web portal for the FDAAA educational initiative ([www.ashpadvantage.com/fdaaa](http://www.ashpadvantage.com/fdaaa)). The activity is approved for 2 hours (0.2 CEUs) of pharmacy law continuing education credit.

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### References

1. 110th U.S. Congress. Food and Drug Administration Amendments Act of 2007. [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_public\\_laws&docid=f:publ085.110](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110) (accessed Apr 22).
  2. Agency for Healthcare Research and Quality and U.S. Food and Drug Administration. Implementation of risk minimization action plans (RiskMAPs) to support quality use of pharmaceuticals: opportunities and challenges; public workshop. <http://www.fda.gov/OHRMS/DOCKETS/98fr/07-2574.pdf> (accessed Apr 22).
  3. U.S. Food and Drug Administration. Sec. 505-1. [21 USC §355-1] Risk evaluation and mitigation strategies. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/FDCAActChapterVDrug-sandDevices/ucm109090.htm> (accessed Apr 22).
  4. U.S. Food and Drug Administration. Questions and answers on the Federal Register notice on drugs and biological products deemed to have risk evaluation and mitigation strategies. <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095439.htm> (accessed Apr 22).
  5. Revlimid package insert. Summit, NJ: Celgene Corporation; January 2009.
  6. U.S. Food and Drug Administration. Questions and answers on medication guides for erythropoiesis-stimulating agents (ESAs). Epoetin alfa (marketed as Procrit, Epogen), darbepoetin alfa (marketed as Aranesp). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109380.htm> (accessed Apr 22).
  7. U.S. Food and Drug Administration. Draft guidance for industry: format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications. September 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> (accessed Apr 22).
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Planned and coordinated by ASHP Advantage.  
Supported by an educational grant from Roche.

