



Risk Evaluation And Mitigation Strategies: The Experts Answer Questions from Health-System Pharmacists

A midday symposium about the risk evaluation and mitigation strategies (REMS) required by the Food and Drug Administration Amendments Act (FDAAA) of 2007 was held at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, on December 7, 2009. Attendees at the midday symposium learned about the impact of the FDAAA and REMS on health-system pharmacy and submitted questions that were later addressed by the faculty in a live webinar conducted on January 19, 2010.

The FDAAA authorizes the Food and Drug Administration (FDA) to require pharmaceutical manufacturers to submit proposed REMS prior to product approval if warranted because of safety concerns.¹ The legislation also authorizes the agency to require post-approval REMS for products that initially did not require REMS if subsequent safety data suggest that REMS are necessary to ensure that the benefits of the drug outweigh the potential risks. Examples of strategies for managing risks associated with potentially harmful drugs include medication guides, communication plans for health care professionals, and elements to assure safe use (ETASU). Special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and use of patient registries are examples of ETASU. Implementation systems (e.g., maintenance of a database of all certified pharmacies or prescribers) may be required in conjunction with ETASU. The FDA has considerable latitude in the REMS requirements it establishes.

The proposed REMS developed and submitted to FDA by manufacturers should include a risk management

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plan that has clear goals to “achieve specific health outcomes or knowledge related to known safety risks.”² In September 2009, FDA issued a draft guidance on the format and content of REMS to provide manufacturers with assistance in developing this plan and other REMS components (Table 1).³

Table 1.

Objectives of FDA Draft Guidance on REMS³

- Provides FDA’s current thinking on the format and content that industry should use for submissions of proposed REMS
- Describes each potential element
- Includes preliminary information on the content of assessments and proposed modifications of approved REMS
- Describes REMS policies for certain regulatory situations
- Informs industry about who to contact within FDA about a REMS
- Indicates FDA Web sites where documents about approved REMS will be posted
- Provides an example of what an approved REMS might look like for a fictitious product

FDA = Food and Drug Administration; REMS = risk evaluation and mitigation strategies

How FDA Determines Which Drugs Need REMS

The list of drugs with FDA-approved REMS is updated periodically, and it was updated most recently on January 4, 2010.⁴ This list has grown since the first REMS were approved in March 2008. There now are 100 listings for 92 unique drugs. Most (74) of these REMS require only medication guides. Only 8 drugs have requirements for ETASU and implementation systems. The list of approved REMS includes drugs approved by FDA before March 2008, including some “deemed drugs” that in the past were the subject of risk minimization action plans (also known as RiskMAPs) and were subsequently “grandfathered.” The number of drugs with approved REMS is expected to increase in the future.

REMS may be established for drug products before or after approval by FDA. Considerations in determining which drugs have REMS requirements are listed in Table 2.

Table 2.

FDA Considerations in Determining Which Drugs Need REMS²

- Considerations in initial drug product approval
- Estimated patient population size
- Seriousness of disease or condition
- Expected benefit of the drug
- Expected or actual duration of treatment
- Seriousness of any known or potential adverse events
- Whether the drug is a new molecular entity
- Considerations after drug product approval
- Availability of new safety information
- New evidence that REMS requirements are needed to ensure that the benefits of a drug outweigh its risks

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There is a growing trend toward establishing REMS requirements for drug classes rather than individual agents. Concerns about the misuse, abuse, and accidental overdose of extended-release opioid analgesics have led to the development of proposed REMS for products containing fentanyl, hydromorphone, oxycodone, oxymorphone, methadone, or morphine.⁵ An industry working group that includes manufacturers of generic products as well as brand name products developed the proposed REMS. The FDA seeks to balance the need for access to these agents with the need to reduce abuse and misuse. Some possible ETASU under consideration for this class of drugs are:

- Certification and training of prescribers
- Certification and training of pharmacists
- Prescriber-patient agreements

Written comments about proposed REMS requirements for extended-release opioids were solicited from interested stakeholders with an initial deadline for submission in 2009. More than 2000 stakeholders submitted comments to FDA, raising many issues and considerable controversy.⁶ In October 2009, FDA reopened the comment period until October 2010 to accommodate stakeholders. An FDA advisory meeting will be held this spring before a final rule about extended-release opioids is published. ASHP is monitoring the development of REMS for extended-release opioids because of the implications for health-system pharmacists and patients and the possibility that REMS requirements for this class of drugs will serve as a precedent for other class-wide REMS. Watch the ASHP Web site for news about the outcome of this meeting and further developments in establishing REMS requirements for this class of drugs.

REMS Requirements for Hospitals

The REMS requirements for hospitals depend on the REMS. Some REMS require that a drug is dispensed only in certain health care settings (e.g., hospitals).² Other REMS may specifically prohibit dispensing of a drug in the hospital setting.

Some REMS include ETASU for drugs with known serious risks that would otherwise be unavailable, and hospitals may play a vital role in providing these ETASU. These ETASU may include one or more of the following⁷:

- 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 certified
- The drug is dispensed only in certain health care settings (e.g. hospitals)
- The drug is dispensed to patients with evidence of safe-use conditions, such as laboratory test results
- Each patient using the drug is subject to monitoring
- Each patient using the drug is enrolled in a registry

Distribution of Medication Guides in the Inpatient Setting

Medication guides are part of the FDA-approved labeling for prescription drugs.⁸ The regulation for medication guides “applies primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional.”⁸ Whether medication guides must be distributed in the inpatient setting is unclear. Many health-system pharmacists assume that inpatient distribution of medication guides is unnecessary unless the REMS specifies that inpatients must receive medication guides. However, ASHP is seeking clarification of this matter from FDA.

FDA Authority and Legal Implications for REMS for Pharmacies

The FDAAA grants FDA the authority to impose penalties on manufacturers who do not comply with REMS requirements. The FDA can consider the drug misbranded, impose civil monetary penalties of up to \$250,000 per violation and up to \$1 million in a single proceeding, and prevent the sale of a drug if a manufacturer fails to comply with REMS requirements.⁹

The FDA does not have authority to enforce REMS requirements for pharmacies. However, pharmacies that fail to comply with REMS requirements may be subject to misbranding violations and civil liability. For example, failure of a pharmacy to dispense a medication guide can lead to a misbranding violation for the pharmacy because the medication guide is considered part of the FDA-approved labeling. If a patient does not receive a medication guide and is injured by a drug, the pharmacy could be held liable in a lawsuit.

Stay Tuned

The drugs and drug classes with REMS requirements and nature of the requirements are subject to frequent change. The implementation of REMS requirements can be time consuming and burdensome for health-system pharmacists. Watch for another ASHP e-newsletter with an update on this matter and information about the practical implementation of REMS in health systems in the coming months.

Coming in 2010

If you missed the Midday symposium “The FDA Amendments Act of 2007: Impact of Risk Evaluation and Mitigation Strategies” and are eager to learn more about this topic, a web-based activity based on the symposium will be available in March. The activity is approved for 2 hours (0.2 CEUs) of continuing pharmacy education. Podcast interviews with the faculty, which were conducted after the live program in Las Vegas, are also available. These activities are available on the activity website (www.ashpadvantage.com/fdaaa).

We Value Your Feedback

If you attended the live symposium in Las Vegas, please complete the post-activity outcomes survey, if you have not done so already. The survey is short, but it is important because it enables us to document changes in practice as a result of the live educational activity. To access the survey click on the button below.

[Take Survey](#)

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