

# REMS Risk Evaluation & Mitigation Strategies review™

Implementing programs to manage medication risks and benefits

## Risk Management: A New Era of Patient Safety

As of January 4, 2010, the US Food and Drug Administration (FDA) had approved Risk and Mitigation Strategies (REMS) for 87 medications.<sup>1,2</sup> For 79 of these 87 medications, only a medication guide (MedGuide) and/or a communication plan are required by the FDA to meet the criteria for REMS. In fact, several pharmaceutical or biotechnology manufacturers seeking either a New Drug Application (NDA) or a Biologic License Application (BLA) are developing REMS as part of their submission to the FDA.<sup>3,5</sup> Furthermore, the FDA has recently announced that long-acting brand and generic opioid medications will be subjected to class-wide REMS, recognizing that while opioid medications are an appropriate and necessary part of pain management, there can be serious risks when these medications are used improperly.<sup>6,7</sup> REMS are an integral tool used by the FDA to ensure benefits of medications outweigh risks, hence allowing the medications to be used safely and appropriately. To understand REMS, we need to take a closer look at the FDA and its role in ensuring the safe use of medications.

### *FDA and Drug Safety: A Brief Historical Perspective*

In 1938, the US Congress passed the Federal Food, Drug, and Cosmetic (FD&C) Act, which required evidence of a drug's safety prior to marketing approval.<sup>8</sup> Since the passage of this law, the FDA has been the primary regulatory body for ensuring that new medications are adequately tested for safety prior to marketing. Another key milestone for the FDA occurred in 1976, when the patient information leaflet or the patient package insert (PPI) was introduced for mandatory distribution with oral contraceptives [21 CFR § 310.501(2009)].<sup>9</sup> Unlike package inserts, which are directed toward healthcare professionals to provide comprehensive product information, the PPI was a new vehicle in patient-friendly language designed to communicate directly with patients about medication risks and key safety issues.<sup>9</sup>

Through the years, the FDA has continued to expand its role in assessing risk and ensuring the safe use of medications. In 1990, the FDA developed guidelines for risk minimization action plans (RiskMAPs), which

were to be implemented by pharmaceutical and biotechnology companies.<sup>10</sup> RiskMAPs were safety programs designed to minimize patient risk when taking certain prescribed medications that have known associated risks, while at the same time optimizing the drug's benefits.<sup>10</sup> The FDA statutory authority to impose these types of safety programs as a condition of approval was limited to products that received accelerated approval. For products that did not receive accelerated approval, the FDA had to rely on "voluntary" commitments from sponsors that the agency would subsequently incorporate into the terms of a product approval. In early 2007, there were approximately 30 approved products with RiskMAPs. RiskMAPs were in place because these products had documented, serious, and preventable safety risks.<sup>10</sup>

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On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA; Public Law 110-85) amended the FD&C Act, and the FDAAA empowered the FDA with significant new responsibilities, as well as formalized a path for the FDA to enforce the regulations.<sup>11-13</sup> Prior to the FDAAA, there had been no accountability measures and programs were voluntary, whereas this act provided the FDA with tools, resources, and enforcement powers to fulfill its mission of ensuring safety. To that end, the FDA developed guidelines for REMS (Figure) that were designed to ensure that the benefits of a drug outweighed its risks, which the FDA applied more broadly to include both potential as well as known risks.<sup>11</sup> This provision went into effect on March 25, 2008.<sup>12</sup>

### *What Is Risk Management?*

The FDA states that "...risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to mini-



**Figure.** Risk Management: An Iterative Process Designed to Maximize the Benefit-to-Risk Ratio

mize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments...<sup>10</sup> In the process of developing a new medication, extensive clinical studies in well-defined, controlled patient populations are designed and performed to identify and assess the safety risks of the drug prior to its approval and marketing.<sup>14</sup> Even with such rigorous premarketing clinical testing, some risks may only become apparent after FDA-approval of a medication, when it is prescribed to tens of thousands or even millions of patients in the general population.<sup>15</sup> Therefore, risk assessment by the FDA continues after the medication is approved and is critical for evaluating and characterizing the medication's risk profile. For the majority of products, routine risk minimization measures in the form of clinical studies, pharmacovigilance, and observational studies are sufficient to supplement risk and benefit data.<sup>10</sup>

REMS enable these medications, which might otherwise not be approved because of safety concerns, to enter the market, thus allowing patients access to potentially beneficial medications while ensuring that safety is maintained...

REMS are employed by the FDA to manage known or suspected serious risk associated with a drug or biologic to ensure that the drug benefits outweigh the risks.<sup>13</sup> REMS use many of the same tools that the earlier RiskMAPs used, but the tools are applied to a broader setting. Like RiskMAPs, REMS ensure the safe use of medications based on known safety risks that have become apparent in clinical trials. However, unlike RiskMAPs, REMS also safeguard against potential safety risks not seen in controlled trials but that may be of concern on the basis of

other factors, such as the mechanism of action or biochemistry of a new drug or biologic. REMS enable these medications, which might otherwise not be approved because of safety concerns, to enter the market, thus allowing patients access to potentially beneficial medications while ensuring that safety is maintained and that patients are informed of possible adverse events.

#### *What Are the Components of REMS?*

All approved REMS must have a timetable for assessment at a minimum of 18 months and 3 years after a strategy is approved, as well as in the seventh year after approval.<sup>11,13</sup> Other assessments at additional time points can be required by the FDA on a case-by-case basis, and these would be specified in the approved strategy.<sup>13</sup> If the FDA determines that serious risks of the medication have been identified and appropriately managed by REMS, additional assessments may be eliminated after the 3-year period.<sup>13</sup>

In addition to a required timetable of assessments to evaluate risks, REMS may also require other elements to mitigate risks.<sup>11,13</sup> A REMS program could include the development and distribution of a MedGuide or a PPI to effectively communicate risks to patients directly and in patient-friendly language. Also, REMS may include a communication plan to healthcare professionals and their organizations. This communication plan may support the implementation of information dissemination related to serious risks, informing healthcare professionals about specific safety protocols, such as laboratory testing to determine patient eligibility for a drug or continued safety monitoring for patients already taking a certain medication.

Additional "elements to assure safe use" may be required if the medication has been shown to be effective but is associated with serious adverse events.<sup>11,13</sup> In these situations, approval of a drug is granted only if these elements are part of a strategy to mitigate specific serious risk(s), as identified in the product label. Otherwise, without the REMS, the medication would not be made available for

**Table. Components of Risk Evaluation and Mitigation Strategies (REMS)**

Required	<ul style="list-style-type: none"> <li>• Timetable for assessments at 18 months, 3 years, and 7 years</li> </ul>
Additional Potential Elements	<ul style="list-style-type: none"> <li>• Medication guide</li> <li>• Patient package insert</li> <li>• Communication plan to healthcare providers</li> </ul>
Elements to Assure Safe Use	<p><b>Certification</b></p> <ul style="list-style-type: none"> <li>• Healthcare providers who prescribe the drug have particular training or experience, or are specially certified</li> <li>• Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified</li> </ul> <p><b>Restricted Distribution</b></p> <ul style="list-style-type: none"> <li>• The drug is dispensed to patients only in certain healthcare settings, such as hospitals</li> <li>• The drug is dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results</li> </ul> <p><b>Tracking</b></p> <ul style="list-style-type: none"> <li>• Each patient using the drug is subject to certain monitoring</li> <li>• Each patient using the drug is enrolled in a registry</li> </ul>
Implementation	<ul style="list-style-type: none"> <li>• Monitor and evaluate implementation by healthcare professionals and work to improve their implementation of REMS</li> </ul>

Sources: References 11 and 13.

use because of its serious associated risks. The “elements to assure safe use” include certification, restricted distribution, and tracking requirements. Specifically, healthcare providers who prescribe a drug with REMS, or pharmacies, practitioners, or healthcare settings that dispense the drug, must have specific training, experience, or a special certification. Dispensation of the drug may be limited to a certain setting (eg, hospital) or restricted to certain patients with evidence or other documentation of safe-use conditions, such as specific laboratory test results. Patient safety may be assessed by imposing mandatory patient monitoring programs or enrolling patients in a safety registry. The FDA may also require that medication manufacturers take reasonable steps to monitor and evaluate implementation by healthcare professionals who are responsible for implementing those REMS elements and to work to improve their implementation (Table).

#### *REMS Requirements for Drugs and Biologic Products*

During the approval process, the FDA determines whether a REMS program is required to ensure that the benefits of the drug or biologic outweigh the risks.<sup>11,13</sup> The FDA must consider several criteria when determining if a REMS program is necessary for products with pending applications and under consideration for approval. The FDA will examine:

- The estimated size of the population that will likely be using the drug
- The seriousness of the disease or condition being treated

- The expected benefit of the drug with respect to that condition
  - The expected duration of treatment with the drug
  - The seriousness of known adverse events reported during clinical trials or the potential adverse events associated with the medication and the background incidence of such events in the population that is likely to use the medication
  - Whether the medication is a new molecular entity.
- The FDA will not approve any drug or biologic products without REMS if the FDA had previously determined that REMS are a necessary strategy.

Several drug and biologic products that previously were approved with RiskMAPs now have REMS.<sup>11,13</sup> Also, REMS may be required for drugs that were already approved before the FDAAA became effective if new safety information becomes available and the FDA determines that REMS are necessary to ensure that the benefits of the drug outweigh the risks. According to the FDAAA, new safety information could be derived from clinical trial data, adverse event report, postapproval study, peer-reviewed biomedical literature, data from a postmarket risk identification and analysis system, or any other scientific data deemed appropriate by the FDA.

#### *Enforcement Authority of the FDA*

The FDAAA has given the FDA the authority to require REMS when necessary to ensure that the benefits of a medication outweigh the risks.<sup>11-13</sup> Furthermore, under the FDAAA, the FDA has authority to impose civil mon-

etary penalties if REMS requirements are not met. The product in question may not be introduced into the market, and, if the product is already on the market, it may be misbranded. Selling the product could potentially expose the sponsor of the drug or biologic to civil enforcement action from the FDA. Civil penalty fines of up to \$250,000 per violation, which are not to exceed \$1 million for all violations adjudicated in a single proceeding, can be imposed. If a violation continues after written notice from the FDA, the FDA will impose penalties of up to \$10 million for all violations adjudicated in a single proceeding.

Unfortunately, implementing REMS processes can be inconvenient for private medical practices or healthcare facilities because complying with REMS (eg, registering a facility and/or patients) often means taking time or other resources away from patient care and associated activities, such as patient education. In addition, implementing REMS processes has resulted in costs, both to the pharmaceutical industry and practicing healthcare professionals, and these costs are not currently reimbursed. Healthcare professionals may be required to track medication doses, enroll patients in registries, or obtain additional patient information required by the REMS.

...(t)he FDA has authority to impose civil monetary penalties if REMS requirements are not met.

Also, because of the certification requirements associated with some REMS programs, there may be additional cost to hospitals and physicians' offices associated with training staff to facilitate prescribing and dispensing through approved REMS programs. Complying with REMS may be a particularly disruptive burden to pharmacists, who may need to develop special ordering procedures or use different suppliers.

Often the FDA has very specific requirements for REMS, depending on the medication in question, and these REMS-specific processes may not be easily adaptable to processes already in place in a medical practice or institution. Because of these constraints, most institutions are, or will be, developing new processes to handle the administration and dispensation of medications with approved REMS. When developing new REMS-related processes, it is essential to develop them with built-in flexibility, thus enabling medical practices or institutions to easily adapt to the specific requirements of the FDA, which are determined on a case-by-case basis and may vary. REMS are far-reaching, and, as such, institutions making REMS-specific process decisions to improve patient care should develop these processes by integrating the expert advice of directors and managers of the medical practice or institution, healthcare professionals who prescribe and dispense medications, and healthcare professionals who support patient care.

REMS are a new way to track and monitor safety. REMS are designed to provide information to ensure

that healthcare professionals have a good understanding of the product label and the evidence concerning known safety risks; this enables healthcare professionals to continue to employ sound medical judgment based on evidence. Thus, REMS support appropriate medical decision-making by the healthcare professional and are not designed to restrict or limit clinical practice or to limit patient access to medication.

In conclusion, REMS are intended to improve patient care by ensuring that the benefits of effective medications outweigh the risks and enable patient access to medications that would otherwise be unavailable. The application of REMS to both new medications and those already on the market continues to grow. Healthcare professionals have a pivotal role in ensuring the successful implementation and assessment of REMS, allowing their patients to continue to benefit from safe and effective medications.

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