



WE ARE NOW MOVING INTO A NEW ERA OF MORE ADVANCED AND FORMAL METHODS TO IDENTIFY AND MITIGATE RISK.

MINIMIZING RISK WHILE PRESERVING BENEFITS: AN INTRODUCTION TO REMS

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Understanding the balance between the benefits and risks associated with a drug therapy is not a novel idea for oncologists—it has long been an essential piece of the treatment planning process. Other stakeholders such as legislators, manufacturers, and patient advocates have also dedicated resources to the ongoing conversation of a drug's availability and utilization versus its clinical risks. At the heart of this continuing debate is the Food and Drug Administration (FDA). Through extensive clinical review, the FDA acts to approve unavailable products, or supplemental uses for existing products, and at the same time educate prescribers and patients to these drugs' associated risks, if such risks exist.

To accomplish this, the FDA has historically required routine risk minimization assessments through vehicles such as product labeling and adverse event reporting and monitoring.

We are now moving into a new era of more advanced and formal methods to identify and mitigate risk. Specifically, some newly approved drugs are entering the market with formal strategies and plans that are designed to minimize a product's risk while preserving its benefits. These same formal plans are also being applied to existing products that have been on the market for several years.

The plans, known as Risk Evaluation and Mitigation Strategies (REMS), are becoming somewhat commonplace—per the FDA, over 20% of approvals from March 2008 to February 2009 required a REMS. Historically referenced as Risk Minimization Action Plans (RiskMAPs), the new name and accompanying acronym signify increased FDA authority to not only monitor drug safety post-product approval but actually prohibit drug approval until a satisfactory REMS is developed. This regulatory authority was gained through the Food and Drug Administration Amendments Act of 2007.¹ In this Act, the FDA was authorized to require manufacturers to design and implement a REMS program for products

with known or potential severe associated risks. The Act also provides the FDA with authority to apply civil monetary penalties if a manufacturer does not remain compliant with the approved REMS.

If it is determined that a product requires a REMS, manufacturers and the FDA engage in discussions that ultimately create the specifics associated with the plan. If the product is premarket, the final approval of the REMS will coincide with the approval of the product—the product does not enter the market without the approved REMS. For drugs that have already been approved and have been subsequently deemed to have serious risks, the manufacturer and FDA can partner to create a REMS that is suitable for that particular product's benefits and risks. Obviously, mature products enjoy market experience that enables the REMS to be designed based on known risks and real-world examples.

THE MANDATORY COMPONENTS OF THE REMS ARE THE ONGOING ASSESSMENTS IN WHICH THE MANUFACTURER AND THE FDA REVIEW THE PLAN TO DETERMINE IF OBJECTIVES ARE BEING REACHED.

To date, the FDA has not provided specific REMS design guidance to manufacturers. However, in general, there are “discretionary” and “mandatory” components of REMS. The mandatory components of the REMS are the ongoing assessments in which the manufacturer and the FDA review the plan to determine if objectives are being reached. Upon review, the REMS can be adjusted. After three years, if it is found that product risks are being managed appropriately through the REMS, the FDA

may eliminate the need for these assessments. The discretionary components of the REMS are broken into four categories:

1. **Medication guide** – distributed to each patient when the drug is prescribed or dispensed.
2. **Patient package insert** – in addition to the medication guide, it can be distributed if the FDA feels this insert will mitigate serious risks.
3. **Communication plan** – can include professional education, dear doctor letters, etc.
4. **Elements to assure safe use** – these are represented in the most thorough REMS plans and can include physician, pharmacist and site certification, patient registries, patient monitoring and data collection, limited distribution, etc. These elements are applied to certain drugs to mitigate risks that would otherwise make the drug unavailable.

During REMS development, the manufacturer will use this outline of components to propose a plan to the FDA. Through ongoing dialogue, the REMS is ultimately crafted to satisfy the FDA and provide a level of security to the agency and the manufacturer that the product is safe for marketing.

Ultimately, the scope of the plan is dependent on the inherent benefits and risks of the product. Therefore, being that all products are unique, many REMS have specifics that are unique as well. Currently, most of the REMS that have been authorized by the FDA only require targeted outreach, such as a medication guide that is provided to prescribers and/or patients. A more thorough REMS includes the “elements to assure safe use” and may require that providers follow certain processes prior to prescribing and/or dispensing the drug. These may require prescribers to receive on-site training, attest to follow REMS guidelines, provide advanced product risk and benefit education to patients. They can also order the product from a limited network of pharmacies and then provide follow-up clinical data at routine intervals.

SINCE EARLY 2008, THE FDA HAS REQUIRED A REMS PROGRAM FOR AN INCREASING NUMBER OF THERAPIES.

To support healthcare providers through these REMS' requirements, manufacturers often offer complimentary support programs to customers to ease access concerns as well as ensure that providers and patients are following guidelines. Depending on the individual REMS, some of the programs may be a required entry point to obtain a product. In general, these programs are available to:

- Explain required documentation, such as provider and patient enrollment or attestations and other necessary forms for data collection.
- Provide direction to access the product, particularly if its distribution is limited to certain channels.
- Communicate via reminder notices to enforce REMS' components such as authorization for subsequent product orders.
- Outreach to capture routine utilization data, some of which is likely shared on an ongoing basis with the FDA.
- Enroll patients into supplemental educational and product access services, such as reimbursement support.

Manufacturer support for healthcare providers and patients is essential to navigating a process that can be cumbersome and therefore resource-intensive. The varying degrees of requirements, paperwork and ongoing monitoring can make it difficult for practices to keep healthcare providers and patients compliant to the components of the REMS. These support programs assist with minimizing REMS costs and offer a helpful partnership throughout the drug's utilization.

With routine approval of these plans, and more to follow, it is also important for practices to be proactive and consider

internally how these will impact daily business. Many practices most likely already have some REMS or other risk management plan experience through products like Promacta, NPlate, Revlimid and Thalomid. Practices are encouraged to take their knowledge from these products and apply them as a core component of doing business as additional REMS loom on the horizon. For example, in February, the FDA sent a letter to manufacturers of certain opioid drugs that indicated a product class-wide REMS will be required. REMS are also currently being developed for certain erythropoiesis-stimulating agents (ESAs).


The importance of this preparation is underscored by the costs that may be associated with REMS. These costs, usually based on the consumption of staff time, can be substantial based on the size of the practice and the number of patients receiving REMS' applicable drugs. Currently, there is no mechanism for offices to be reimbursed for satisfying REMS' requirements, so efficiency will be the key to remaining compliant and continuing patient access to therapy. To prepare for long-term participation in REMS plans, some practice considerations are:

- **Awareness** – how the practice learns of new REMS requirements surrounding currently prescribed products or newly approved products. Routine surveillance of FDA activity through the safety section of their Website is recommended (www.fda.gov).
- **Logistics** – determine the associate(s) who are responsible for keeping REMS-related documentation as well as keeping it in an accessible place for all relevant practice associates.
- **Systems** – REMS requirements associated with products must be accessible in daily tools such as patient charts, treatment guidelines, etc.

- **Resource consumption** – gain an understanding of the staff time consumed to support patients on products with a REMS; this may require shifting some responsibilities to other practice employees.

To date, practices with greater REMS experience or other risk management plans have found that establishing a single point of contact for all requirements is paramount in meeting all associated requirements. This person is knowledgeable of the general process and is available to answer questions, surveys and other required data collection aspects of the REMS plan. Through initial research community-based practices, this role is typically filled by many practices by a nurse or pharmacist who act to capture and disseminate all data and information and fulfill other enrollment requirements.

Since early 2008, the FDA has required a REMS program for an increasing number of therapies. Into 2009, it does not appear that the frequency of approval of these plans are slowing, making it vitally important for both academic and community practices to become comfortable with the REMS concept and the unique aspects of each. Incorporating the time and staff to participate in these plans will continue to apply pressure to practice resource constraints, however, by doing so the practice can continue to ensure that patients have appropriate access to all treatment options. ■



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References:

1. Public Law 110-85