Risk Evaluation and Mitigation Strategies (REMS) and Reaching the Market

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Introduction
Since 2007, the U.S. Food and Drug Administration (FDA) has had legal authority under the FDA Amendments Act to require a risk evaluation and mitigation strategy (REMS) from manufacturers to ensure that the benefits of drugs and biologics outweigh their risks. Even before then, REMS were initiated as early as 1988 involving special programs to detect adverse events relating to the use of Accutane® (isotretinoin), Clozaril® (clozapine) and thalidomide to name some of the earliest.

REMS are required risk management plans that use risk minimization strategies in addition to the professional labeling to ensure that the benefits of certain prescription drugs, including their generic versions, outweigh their risks. The FDA has required REMS for more than 200 drugs since 2007. A list of currently approved REMS can be found on the FDA’s website.

Some examples of the types of risks that REMS aim to mitigate that cannot adequately be addressed merely by the standard prescribing information include risks for serious infections, severe allergic reactions, liver damage and severe birth defects. REMS often involve placing special controls over prescribing, shipping and dispensing the drug; special information disclosure to patients; and other measures intended to address unique safety risks associated with a particular drug or class of drugs.

As the FDA states in its guidance, “no two REMS are exactly alike.” REMS are imposed when the FDA determines that special measures are needed to ensure that the benefits of a drug outweigh the risk. The risk may be, and often is, a known risk that is documented in the drug’s label but mere disclosure in the label is deemed insufficient to protect patients. Often, REMS are used to help mitigate risk for products with black box warnings — the sternest warnings possible for drugs on the market in the U.S. The combination of a REMS with a black box warning is generally used when the FDA deems that the warning is inadequate by itself to provide for the safe use of the product.

Elements of REMS in Practice
All REMS incorporate a requirement for periodic submission of assessment of the REMS to the FDA. REMS also often incorporate elements like a medication guide or patient package insert, a communication plan, elements to assure safe use (ETASU) and an implementation system. Most often a REMS for an abbreviated new drug application (ANDA) usually excludes the communication plan as these later entrants to the marketplace benefit from the communication plan initiated by the innovator company. However, coordination of REMS activities between the innovator and generic sponsors have often proven a bit difficult.

Medication Guide
When a medication guide is included as part of the REMS, the FDA will require the guide to be dispensed with the drug. The guide must be written in non-technical language in a standardized, readable format and is provided in addition to the consumer medication information (CMI).
Communication Plan
The communication plan is intended to inform key audiences, such as health care providers, about the risks of the drug. Such communication plans often include “Dear health care provider” letters, and information about the risks of the drug and measures to ensure safe use is often disseminated through professional societies. A communication plan is intended to educate, inform and raise awareness of risk broadly.

Elements to Assure Safe Use (ETASU)
ETASUs are medical interventions or other actions by health care providers that are required prior to the prescribing or dispensing of the drug to the patient. ETASUs can also be required in order for a patient to continue on treatment. In practice, ETASUs are the most extensive elements of most REMS programs. These ETASUs are intended to reduce specific serious risks listed in the labeling of the drug.

Depending on the individual product and its inherent risk, REMS may require one or all of the following ETASUs:

- Special training and certification for prescribers
- Special certification for dispensers of the product (pharmacies, practitioners or health care facilities)
- Restriction of dispensing to certain health care settings
- Restricting drug to be dispensed only after evidence of safe continued use is gathered, e.g., laboratory testing
- Enrollment of patients in a comprehensive registry
- Individual monitoring of each patient

Timetable for Assessments
The FDA’s timetable for evaluating the effectiveness of a REMS sets minimum requirements at 18 months, three years and seven years after the REMS is approved. The assessment of REMS may be used at any point in time to modify the REMS, with FDA approval of course. In practical experience, numerous REMS, to date more than 140, have been released from their REMS’ requirements — many REMS were eliminated after three years as not being necessary to protect patients. (See the FDA’s list of Released REMS.)

Impact of REMS on Generic Drug Development
Developing a generic version of a drug subject to REMS may be complicated by a number of the individual elements of the REMS: Limits on distribution may make obtaining clinical supplies quite difficult; the requirement for certification of prescribers can severely limit the potential investigator pool; and the requirement for patient registration and medication guides can add to the complexity of the informed consent process. These are just a few of the most apparent considerations that need to be factored when considering the development of generic versions of drugs with REMS.
Because each REMS is unique and tailored to the particular drug, it is important to critically review the REMS and determine which elements need to be carried into the clinical development program for the generic version and which elements will necessarily be carried forward into the commercial plan for the generic drug. Typically, all REMS provisions, with the possible exception of the communication plan, are expected to be duplicated for the generic version of the REMS product.

**Conclusion**

Certain drugs with highly significant risk profiles would not be available in the marketplace if not for the additional protections provided by REMS. Since 2007, the FDA has required REMS for more than 200 drug products, including some that were newly approved and many that were already approved but had potential safety concerns. The ETASUs are often the difference between whether it is reasonable to allow access to a drug at all. Though moving forward with a product that will require a REMS does take additional steps to meet FDA requirements, REMS often are not a permanent requirement. Of the more than 200 REMS approved, more than 140 have been discontinued as no longer necessary to protect patients.

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