**What Is a Risk Management Plan?**

In many countries, special medicine safety plans may be required as part of a medicine’s approval process and to retain its approved status. For instance, these plans are required by:

- The U.S. Food and Drug Administration Amendments Act of 2007 (FDAAA) and the FDA’s *Guidance for Industry Format and Content for Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* (see sidebar).

Even prior to the enactment of such legislation and regulations, pharmaceutical companies—recognizing that clinical studies do not necessarily represent real-world experience—often designed Risk Management Plans in the pre-approval stages of developing new medicines and have included them in submissions for approval. This type of plan, or system, may be defined as a set of pharmacovigilance activities designed to identify, characterize, prevent, or minimize risks related to the medicine; to assess the effectiveness of those interventions; and to communicate those risks to patients and health care providers.

In Europe, Risk Management Plans (RMPs) are now routinely required by EMA as part of the medicine approval process. An RMP includes a

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<th>Risk Evaluation and Mitigation Strategy (REMS)</th>
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<td>A REMS is developed to help ensure that the benefits of a medicine outweigh its risks. A REMs may be required by the FDA as part of the approval process for a new product, or for an approved product when new safety information emerges. An applicant may also voluntarily submit a REMS. Some medicines that were previously approved with Risk Minimization Action Plans (RiskMAPs) are now deemed to have a REMS.</td>
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A REMS is a strategy to manage a known or potential serious risk associated with a medicine. Its purpose is to allow patients continued access to certain medicines for which there are safety concerns that may be managed through appropriate use. All REMS must include a timetable for assessment of the REMS. A REMS may also include one or more of:

- A Medication Guide. (This may also be a stand-alone requirement.)
- A patient package insert.
- A communication plan to disseminate information to health care providers in support of the strategy.
- Elements to Assure Safe Use (ETASUs) of the product, such as:
  - Special training or certification for health care professionals who prescribe or dispense the medicine.
  - Dispensing the medicine only in certain settings (e.g., in a hospital) or with evidence of safe use conditions (e.g., laboratory test results).
  - Monitoring or registration of each patient using the medicine.
- An implementation system for certain elements to ensure safe use.

Proposed revisions to an existing REMS may be submitted based on the results of assessments or when new safety information arises.
What Is a Risk Management Plan? (cont’d)

summary of important identified risks of the medicine, potential risks, and missing information—this serves as the basis for an action plan for pharmacovigilance and risk minimization activities. This summary incorporates the safety profile of the medicine at that time in its life-cycle, either during preclinical testing, pre-approval clinical development, or pre-approval. Data on known and potential safety risks (drawn from preclinical and/or clinical study results for the medicine) are specified; the extent and limitations of the safety database (kinds of studies, numbers of subjects, rigor of study designs, exclusions in study protocols, etc) are defined; and areas of risk that have not yet been studied or not studied extensively (such as specific [or larger] patient populations, patients with other medical conditions or in other treatment settings, interactions with other medications) are identified.

Pharmacovigilance and risk management activities that might be included in an RMP fall into two categories: routine activities—which would generally be conducted for any medicine at the same stage of development where no special safety concerns have arisen—and additional activities designed to address identified safety concerns (as highlighted in the summary). Routine pharmacovigilance would include the safety evaluations incorporated in clinical trials and the monitoring and reporting of spontaneous adverse events pre-approval. Routine risk management activities would include ensuring that suitable warnings are included with all product information and careful labeling and packaging of the medicine.

In an RMP, the action plan might include calling for additional pharmacovigilance in the form of:

- Active surveillance (e.g., medical records reviews, patient or physician interviews, prescription event monitoring, data from disease or drug exposure registries).
- Epidemiology studies (retrospective or prospective).
- Further clinical studies (specific safety studies, larger studies over longer periods).
- Drug utilization studies (which describe how a drug is marketed, prescribed, and used in a specified population—often stratified by age, gender, concomitant medications, etc—and how these factors influence clinical, social, and economic outcomes).

If the action plan specifies additional risk minimization activities, these could include:

- Additional educational material about the medicine and its use (patient information brochures, visual aids, physician prescribing guides/checklists, pharmacist dispensing guides/checklists, health care provider letters).
- Training programs (patient- or physician-oriented).
- Restricted use of the medicine (e.g., for use/dispensing only in hospital, or where specific equipment [e.g., resuscitation equipment] is available; availability only in limited unit sizes).