SAFETY RISK MANAGEMENT:

A FRAMEWORK FOR DEVELOPING AND IMPLEMENTING REMS MODIFICATIONS AND REVISIONS

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Rapidly evolving safety risk management processes increasingly dictate drug approval and post-marketing surveillance[1]. To meet FDA requirements of developing and implementing changes to risk-evaluation and mitigation strategies (REMS), and to streamline this complicated process, we have detailed a framework of key concepts, standards and submissions procedures.

In 2007, the FDA Amendments Act (FDAAA), which amends the Federal Food, Drug and Cosmetics Act (FFDCA) to include post-market safety activities within the process for the review of human drug applications or supplements, introduced REMS to assure safe use of certain drugs. As defined by the FDA, "A REMS is a required risk management plan that uses tools beyond the prescribing information (the package inserts) to ensure that all benefits of certain drugs outweigh their risks" (U.S. Food and Drug Administration, 2019, p. 2). Without REMS some drugs could not be approved because of high safety risks. Prior to the REMS programs, a few products used risk minimization action plans (RiskMAPs) to the same end[2]. REMS supersedes RiskMAPs. The most extensive components of a REMS program are elements to assure safe use (ETASU), developed to mitigate specific and serious risks. Examples of common ETASU include:

- Prescribing physicians require more training or certification (e.g., to mitigate risk of severe allergic reaction)
- Patient monitoring for evidence of safe-use conditions (e.g., liver function monitoring to mitigate risk of liver damage, pregnancy screening with a negative result to mitigate risk of severe birth defects)
- Required enrollment in patient registry

Safety measures of a REMS are unique to a drug's associated safety risks. The FDA can require a REMS at any time, pre- or post- approval, and a REMS can be required for a single drug, or for a class of drugs. While the FDA is responsible for reviewing and approving REMS programs, sponsors are responsible for developing them. When deciding if a REMS is needed, consider the following factors[3]:

- Population size
- Seriousness of the disease
- Expected benefit
- Expected treatment duration
- Seriousness of known or potential adverse events
- Novelty of the drug

REMS REVISIONS, MINOR MODIFICATIONS AND MAJOR MODIFICATIONS

When new safety information becomes available, changes to a REMS may be proposed to ensure that a drug's risk-to-benefit ratio is acceptable. Changes to a REMS may also be proposed to reduce the burden on healthcare professionals of complying with the REMS. Changes to REMS are categorized as REMS revisions, minor REMS modifications and major REMS modifications, depending on degree of potential effect on serious risk, safe use and the actions necessary to comply with the REMS[4]. Each REMS category has different submission criteria and regulatory action requirements (See Table 1 below).

TABLE 1. SUBMISSIONS CRITERIA, EXAMPLES AND REGULATORY ACTION FOR REMS CHANGES[4]

	Criteria	Examples	Regulatory Action
REVISIONS	> Changes are editorial in nature, and > Do not affect information in REMS materials regarding serious risk or safe use, and > Do not affect actions that must be taken in order to comply with the REMS	> Updates to contact information > Changes to International Classification of Diseases code > Changes to approved package count configuration requiring changes in the REMS materials	> REMS revisions must be submitted in the annual report
MINOR MODIFICATIONS	> Changes have a limited effect on information in REMS materials regarding serious risk or safe use, and > Changes have a limited effect on actions that must be taken in order to comply with the REMS	> Adding an approved new strength or dosage regimen > Adding an authorized generic > Graphics changes, including logo changes > Changing REMS call center hours of operation	> REMS minor modifications must be submitted as a changes being effected in 30 days (CBE-30) supplement
MAJOR MODIFICATIONS	> Changes have a substantial effect on information in REMS materials regarding serious risk or safe use, and > Changes have a substantial effect on actions that must be taken in order to comply with the REMS > Or safety labeling changes that modify a REMS	> Changing an element to assure safe use (ETASU) that modifies the verification process for dispensing the drug > Changing language in prescriber training materials to include safety labeling changes made to the package insert	> REMS major modifications must be submitted as a prior approval supplement (PAS)

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ESSENTIALS TO SUBMITTING AND IMPLEMENTING PROPOSED REMS CHANGES[4]

1. If needed, seek advice from the FDA before submitting a proposed REMS modification.
2. Include a REMS history outlining all changes made to the REMS since original approval.
3. For minor and major modifications, except for FDA-required submissions, submit adequate rationale for the change. Detailed instructions for specific causes are provided in the FDA's Guidance for Industry, Risk Evaluation and Mitigation Strategies: Modifications and Revisions (U.S. Food and Drug Administration, 2019, p.13).
4. REMS revisions can be implemented immediately upon FDA receipt of the submission; no action is required from the FDA for this type of change.
5. Minor modifications can be implemented 30 days after FDA receipt of the submission; however, the FDA has 60 days from receipt of the submission to review and act on minor modifications; therefore, changes are not considered final until FDA approval.
6. Major modifications cannot be implemented until the FDA approves the proposed changes. The FDA has 180 days after receipt of the submission to review and act on proposed major modifications, with the exception of major modifications due to safety labeling changes that are considered conforming. In this instance, the FDA has 60 days after safety labeling changes are approved to review and act on the proposed major modifications. The 180-day time frame, following approval of the safety labeling changes, applies to major modifications due to safety label changes that are not considered conforming.
7. REMS for NDAs and BLAs require assessment of effectiveness of its safety measures at 18 months, three years and seven years after a REMS is approved, documented in a timetable to be included in the submission application. Assessments inform sponsors of the necessity of continuing a REMS program or modifying it.

CHALLENGES TO THE DEVELOPMENT AND IMPLEMENTATION OF REMS

- Developing and implementing a REMS program is time-consuming and costly, which affects sponsors, healthcare providers and patients.
- No two REMS programs are alike; each has different requirements and challenges.
- Added REMS requirements can unduly burden patients and providers.
- Recently published FDA draft guidances direct sponsors through the development of a REMS assessment plan and the execution of REMS assessment surveys, however these tasks remain difficult and intimidating.

CHALLENGES TO REMS DEVELOPMENT AND IMPLEMENTATION DUE TO A PUBLIC HEALTH EMERGENCY (COVID-19)[5]

During and for the duration of a public health emergency (PHE), the FDA may impose temporary policies for certain REMS requirements. To ensure that timely response efforts meet patient needs in such situations, healthcare professionals, sponsors, regulators and other relevant parties should closely monitor FDA announcements and communicate with the FDA if needed.

In March 2020, specific to the COVID-19 pandemic, the FDA issued a new guidance addressing completion of REMS program ETASU requirements that may negate public health interventions for self-isolation and quarantine. This guidance states that laboratory testing or imaging studies required by some REMS can put patients and the public at risk of COVID-19 transmission and advises that "healthcare providers prescribing and/or dispensing these drugs should consider whether there are compelling reasons not to complete these tests or studies during the PHE, and use their best medical judgment in weighing the benefits and risks of continuing treatment in the absence of laboratory testing and imaging studies." (U.S. Food and Drug Administration, 2020, p. 7). The guidance indicates that these accommodations should be documented and summarized in the REMS Assessment Report.

As information becomes available on COVID-19 and safety risk management, other temporary policies for certain REMS requirements may arise.

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TAKEAWAY MESSAGE

We cannot over-emphasize the importance of safety risk management. Regulators have expanded submissions requirements to include REMS programs for certain high-risk products to maintain patient safety, and sponsors must keep up with the rapidly evolving changes. To navigate complex REMS requirements and challenges, let Amarex's safety and pharmacovigilance experts plot your REMS strategy course. We have extensive experience designing, executing and managing a broad range of REMS programs across many therapeutic areas. Dedicated to patient safety, our staff proactively track risk-management-related regulatory, legislative and market concerns, keeping us ahead of safety issues. Since 1998, Amarex has developed efficient, cost-effective product development solutions, tailored to our clients' needs.

References

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For more information, contact **healthsciences@nsf.org** or visit **www.nsfhealthsciences.org**

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