On September 21, 2016, the US Food and Drug Administration (FDA) issued Draft Guidance for Industry: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary, which is intended to clarify how the FDA will determine whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.

In Depth

On September 21, 2016, the US Food and Drug Administration (FDA) issued draft guidance—Draft Guidance for Industry: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary (Draft Guidance)—intended to clarify how the FDA will determine whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.

The Food and Drug Administration Amendments Act of 2007 (FDAAA) authorizes FDA to require a REMS for a drug if FDA determines a REMS is necessary to ensure that the benefits of a drug outweigh its risks. See 21 U.S.C. 355-1. A REMS may include:
- Medication Guides;
- Patient package inserts;
- Communication plans; and
- Elements to assure safe use (ETASU), such as requirements that:
  - Prescribers have particular training or experience;
  - Patient use be monitored;
  - The drug be dispensed upon evidence or other documentation of safe use conditions; and
  - A system be implemented to allow sponsor monitoring and evaluation.

The FDAAA further requires the FDA to consider six factors when deciding whether to require a REMS. In the Draft Guidance, the agency outlines how it intends to apply these six factors:

1. **The seriousness of any potential or known adverse events (AEs) and the background incidence of such AEs in the population likely to use the drug.** The more serious a drug’s known or potential associated risks relative to its benefits, the more likely it is that a REMS will be necessary. FDA will consider the source, nature and reliability of available scientific evidence about the adverse events, as well as the characteristics of the risks, including the severity, frequency, temporality, preventability, reversibility, background incidence and likelihood of occurrence of the adverse events.

2. **The expected benefit of the drug.** FDA may evaluate information about the drug’s effectiveness, whether the drug treats a serious disease or condition, whether it fills an unmet need and whether it can cure the disease or alleviate its symptoms. FDA may also consider the extent to which a new dosage form enhances convenience of administration and/or improves adherence to prescribed regimens, and whether new formulations or delivery mechanisms may extend treatment to patient populations who were formerly unable to use the drug.

3. **The seriousness of the disease or condition to be treated.** The more serious the disease or condition, the greater the potential benefit of the drug in the benefit-risk assessment. Even for drugs intended to treat serious or life-threatening diseases or conditions, however, the severity, irreversibility or duration of an associated risk may support the establishment of a REMS.

4. **Whether the drug is a new molecular entity (NME) (or a new Biologic).** Information about NMEs and new Biologics License Applications (BLAs) may be limited, and as a result, there may be greater uncertainty about the risks associated with the use of such products that may emerge in a post-approval setting. Depending on the nature of the uncertainty (e.g., strength of association of adverse event with drug treatment, likelihood of occurrence), FDA may require a REMS.
5. The expected or actual duration of treatment. If long-term therapy with a drug appears to increase the likelihood of serious adverse events, FDA may require a REMS to limit the duration of treatment or to ensure that patients on long-term treatment are monitored. A REMS may also be required for a drug with a relatively short duration of treatment, however, depending on the nature of the associated risk.

6. The estimated size of the population likely to use the drug. FDA considers the extent to which the population likely to use the drug includes a significant number of patients expected to use the drug for unapproved uses and the risks and potential benefits associated with those uses. In cases where the risks associated with unapproved uses are significant in relation to potential benefits, FDA may consider whether a REMS designed specifically to mitigate the risks associated with those uses is appropriate.

In the Draft Guidance, FDA explains that no single factor is dispositive and its determination about whether a REMS is necessary is a “complex, drug-specific inquiry.” For example, FDA indicates it also takes into account existing REMS for drugs with similar risks; whether the REMS is compatible with established drug distribution, procurement and dispensing systems; and the consequences of treatment interruptions or delays that may be created by a REMS.


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