haynesboone

April 26, 2019

FDA's Risk Evaluation Guidance Brings Clarity, Not Solutions

By: Paul Dietze and Elizabeth Crompton

This April, the U.S. Food and Drug Administration issued final guidance clarifying how the FDA applies the factors in section 505-1 of the Federal Food, Drug and Cosmetic Act[1] to determine whether a risk evaluation and mitigation strategy is necessary to ensure that the benefits of a drug outweigh its risks.

Section 505-1 of the FD&C Act was created as part of the Food and Drug Administration Amendments Act of 2007. A REMS is a required risk management plan to ensure that the benefits of a drug outweigh its risks.

To approve a drug, the FDA must determine that the drug is safe and effective for its labeled indications under its labeled conditions of use.[2] The REMS guidance notes that "FDA's determination that a drug is safe, however, does not suggest an absence of risk" and that "a drug is considered safe if it has an appropriate benefit-risk balance."[3]

A major factor in assessing benefits vs. risks is management of those risks, including both risk assessment and risk minimization. This is an iterative process that involves: "(1) assessing a drug's benefit-risk balance, (2) developing and implementing tools to minimize the drug's risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to risk minimization tools to further improve the benefit-risk balance."[4]

The process continues throughout a drug's life cycle, as the results of risk assessment inform the sponsor's decisions regarding risk minimization.[5]

Risk mitigation is intended to preserve a drug's benefits while simultaneously reducing the risks as much as possible.[6] Although routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits for most drugs while minimizing risks, additional interventions beyond the FDA-approved labeling may be necessary to ensure that the drug's benefits outweigh its risks.[7]

In such a situation, the FDA may determine that a REMS is necessary to ensure an appropriate benefit-risk balance. The FDA can require a REMS at any time, from before a new drug is approved to after approval.[8] If a REMS cannot mitigate the risks associated with a drug such that the benefit would exceed the risks, the FDA will not approve the drug.[9]

If the FDA determines that a REMS is required as part of the risk management plan, the FDA may require one or more REMS elements such as a medication guide, a patient package insert and/or a communication plan.[10] In certain situations in which a drug has been shown to be effective but is associated with a specific serious risk that would weigh against approval, the FDA may further require that the REMS includes elements to assure safe use, or ETASU, to mitigate the risk.[11]

The ETASU can include one or more of the following requirements:

- Health care providers who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;

- The drug be dispensed to patients only in certain health care settings, such as hospitals;
- The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
- Each patient using the drug be subject to monitoring; or
- Each patient using the drug be enrolled in a registry.[12]

A REMS that includes an ETASU may also include an "implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the elements," such as, for example, the development of a REMS-specific web site or call center to facilitate enrollment and the establishment of electronic databases of certified health care settings.[13] In general, all REMS should include one or more overall goals, which, in the case of a REMS with ETASU should be directed to the specific risk the ETASU are designed to mitigate.[14]

If the FDA determines that a REMS is needed, the FDA will consider the goals of the proposed REMS to address the risks and what specific REMS elements could help meet those goals.[15] The REMS should be "designed to meet the relevant goals, not unduly impede patient access to the drug, and minimize the burden on the health care delivery system to the extent practicable."[16]

The REMS must also include a timetable for submission of assessments of the REMS, which usually will occur at 18 months, 3 years and 7 years after the REMS is approved.[17]

The REMS guidance explains that determining whether a REMS is necessary for a particular drug is "a complex drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case. In conducting this analysis, the FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks."[18]

When determining if a REMS is needed, the FDA considers information from a variety of sources, including, for example, the FDA's internal and external experts; input on relevant issues from other centers in the FDA, other government agencies, advisory committee meetings, the Drug Safety Oversight Board, literature, and professional societies.[19]

For approved drugs the FDA also considers information from post-approval clinical trials and other post-approval studies, including post-approval adverse event reports and active surveillance.[20]

In considering whether to require a REMS and what type of REMS should be required, the FDA considers the following six factors, as required by Section 505-1(a)(1) of the FD&C Act:

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- The expected benefit of the drug with respect to the disease or condition;
- The seriousness of the disease or condition that is to be treated with the drug;
- Whether the drug is a new molecular entity;
- The expected or actual duration of treatment with the drug; and
- The estimated size of the population likely to use the drug.[21]

All six factors are considered together, and no single factor is determinative as to whether a REMS is necessary.[22]

The REMS guidance discusses the application of each factor.[23]

The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events 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.”[24]

The REMS guidance then provides examples. For example, for a drug that is associated with an adverse event that is reversible or preventable, the REMS may require monitoring the patient through laboratory studies to determine if the adverse event is present.[25]

On the other hand, a drug that is associated with an adverse event that is irreversible (e.g., that causes a permanent disability or persistent incapacity) may require a REMS that mandates a prescriber training and patient counseling on the associated risks and the drug’s benefit-risk calculations so as to “facilitate informed patient and prescriber decisions about treatment with the drug.”[26]

The FDA will also consider the frequency and severity of adverse events associated with the use of a drug.[27] A high frequency of adverse events can necessitate a REMS, as can an infrequent adverse event, if the adverse event is particularly severe.[28]

As part of its evaluation of whether a REMS is needed, the FDA also considers additional factors, including: availability of information about managing the risk; implementation of risk management measures; the specialties of the health care providers who prescribe, dispense, and administer the drug; health care professional familiarity with approaches to mitigate the risk; the health care setting(s) in which the drug is used or is likely to be used; and, for drugs used in an outpatient setting, the degree to which patients can be expected to reliably recognize symptoms as being associated with a drug and to take necessary actions to address adverse events.[29]

The Expected Benefit of the Drug with Respect to the Disease or Condition

In evaluating a drug’s benefit, the FDA considers information about the drug’s effectiveness, the seriousness of the disease or condition treated, whether it fills an unmet medical need and whether it can cure the disease or alleviate its symptoms.[30] For new dosage forms, the FDA may also consider “the extent to which the new dosage forms enhance convenience of administration and/or improve 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.”[31]

The drug’s benefits, however, are balanced against the risks associated with its use.[32] As an example, the REMS guidance notes that, although a once-a-month dosage form may offer benefit in that it is more convenient and leads to better patient compliance, it may have a different risk profile that would warrant a REMS.[33]

The Seriousness of the Disease or Condition That Is to be Treated With the Drug

The FDA also considers the seriousness of a disease or a condition.[34] “[T]he more serious the disease or condition to be treated, the greater the potential benefit of the drug’s measured effect in the benefit-risk

assessment."[35] However, even for drugs intended to treat serious or life-threatening diseases or conditions, an associated risk may be sufficiently severe, irreversible or long to warrant a REMS.[36]

Whether the drug is a new molecular entity. For new molecular entities or certain biological license applications, information about the drug may be limited and, thus, there can be greater uncertainty about risks associated with its use.[37] When safety information about a NME or BLA indicates a serious risk and there are uncertainties about the nature of the serious risk, a REMS may be required to assure that the benefits of the drug outweigh its risks.[38]

The Expected or Actual Duration of Treatment With the Drug

A REMS may be necessary when long-term therapy with a drug appears to increase the likelihood of a serious adverse event.[39] Such a REMS would likely limit the duration of treatment or ensure that patients on long-term treatment are monitored for the adverse event.[40]

A REMS could also be necessary for a drug with a relatively short duration of treatment.[41] For example, if a drug is associated with an adverse event immediately after administration, a REMS may limit administration to a setting where the patient can be monitored so that the adverse event, if it were to occur, can be properly managed.[42]

Likewise, a REMS may require specialized training for drugs that are can have adverse effects if improperly administered.[43] In cases where adverse events can occur after drug treatment has ended, a REMS may be required to ensure proper monitoring of patients for a sufficient time after treatment has concluded.[44]

The Estimated Size of the Population Likely to Use the Drug

The FDA will consider whether the expected patients are likely to use the drug for unapproved uses, and what are the risks associated with those unapproved uses.[45] A REMS can be designed to ensure that a drug's use is limited to its approved indication.[46]

After discussing the six factors identified in section 505-1(a)(1) of the FD&C Act, the REMS guidance then identifies burdens on the health care delivery system and patient access relating to REMS.[47] The REMS guidance states that "FDA understands that REMS, particularly those with ETASU, may impose some measure of burden on patients and/or health care providers," and the FDA considers these factors when deciding whether a REMS is necessary.[48]

In particular, some of the factors the FDA considers include existing REMS elements for other drugs with similar risks; whether the REMS under consideration can be designed to be compatible with already-existing drug distribution, procurement and dispensing systems; access to healthcare for patients for whom the drug is indicated and whether the REMS may impose additional access difficulties; and the consequences of potential treatment interruption or delays, particularly where patients have serious or life-threatening conditions and/or have difficulty accessing health care.[49]

The REMS guidance further notes that the selection of REMS elements and tools can be influenced by the extent to which they have already been used in clinical trials to evaluate the drug's safety and efficacy and by regulatory precedent for addressing similar risks.[50]

The REMS guidance concludes: “FDA also encourages sponsors to submit REMS proposals that are compatible with established distribution, procurement, and dispensing systems. Following approval of a REMS, FDA continues to evaluate the impact of the REMS on patient access and the health care delivery system.”[51]

Although REMS are an important means for minimizing the risk associated with drugs, REMS programs have come under scrutiny, including by outgoing FDA Commissioner Scott Gottlieb for delaying entry of generics into the marketplace.

As noted in an April 4, 2019, FDA statement entitled "FDA In Brief: FDA affirms its commitment to efficient adoption of Risk Evaluation and Mitigation Strategy plans and to making sure they do not impede generic drug development," Gottlieb, discussing the REMS guidance, stated that “[w]hile REMS are a critical tool designed to reinforce medication use behaviors and actions that support the safe use of that medication, some companies also try to game the system and use REMS to delay the entry of generics.”[52]

The FDA statement noted: “In some cases, branded sponsors have refused to sell samples of brand products with REMS with ETASU impacting distribution of the drug to potential generic competitors. Generic drug developers need the samples of the brand drug to develop their generic product and to conduct testing to show that their product is bioequivalent to the brand drug for FDA approval. The FDA cannot stand idly by and allow companies to abuse the system, frustrating generic drug manufacturers and ultimately keeping patients from accessing lower cost generic drugs.”[53]

Although the REMS guidance does not address this abuse, the FDA statement noted that in May 2018, the FDA “made available a list of companies that have potentially been blocking access to the samples of their branded products” and that the FDA will continue to update this list “to help deter companies from using REMS as an excuse.”[54]

Congress has also been interested in abuses of the REMS system to hinder generic competition. Both the House and the Senate are again considering the CREATES Act, which aims “[t]o promote competition in the market for drugs and biological products by facilitating the timely entry of lower-cost generic and biosimilar versions of those drugs and biological products.”[55]

Congress stated that REMS abuses include the practice of using REMS distribution restrictions “as reasons to not sell quantities of a covered product to generic product developers, causing barriers and delays in getting generic products on the market.”[56] Among other things, the CREATES Act would allow a generic or biosimilar pharmaceutical manufacturer to sue the brand sponsor if the brand sponsor refuses to sell them the samples needed to develop a generic or biosimilar version of the brand drug.[57]

The FDA’s REMS guidance provides useful information to pharmaceutical manufacturers about the basis for adopting a REMS and the considerations involved. However, the REMS guidance itself does not affect any of the potential abuses in which Congress seems so interested. Whether the CREATES Act gains any traction and causes change is yet to be determined.

First published by *Law360* on April 26, 2019.

[1] 21 U.S.C. § 355-1

[2] REMS Guidance at 4.

[3] Id.

[4] Id.

[5] Id.

[6] Id. at 4.

[7] Id.

[8] Id. at 3.

[9] Id. at 5.

[10] Id. at 2.

[11] Id.

[12] Id.

[13] Id.

[14] Id. at 3.

[15] Id. at 5.

[16] Id.

[17] Id. at 3.

[18] Id. at 4.

[19] Id. at 4-5.

[20] Id. at 5.

[21] Id. at 5.

[22] Id.

[23] Id. at 5-9.

[24] Id. at 6.

[25] Id.

[26] Id.

[27] Id.

[28] Id.

[29] Id. at 7.

[30] Id.

[31] Id.

[32] Id.

[33] Id.

[34] Id. at 8.

[35] Id.

[36] Id.

[37] Id.

[38] Id.

[39] Id. at 9.

[40] Id.

[41] Id.

[42] Id.

[43] Id.

[44] Id.

[45] Id.

[46] Id.

[47] Id.

[48] Id.

[49] Id.

[50] Id. at 10.

[51] Id.

[52] FDA Statement.

[53] Id.

[54] Id.

[55] CREATES Act of 2019, S. 340, H.R. 965, 116th Cong.

[56] Id. at § 2(6).

[57] Id. at § 3(b)(1).