FDA Releases Initial Draft Guidance on Risk Evaluation and Mitigation Strategies (REMS): Seeking Input from Stakeholders

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written by Paul T. Kim, Kalah Auchincloss, James M. Flaherty, Jr., Maia M. Larsson

The Food and Drug Administration (FDA) announced on September 30 that it has released a draft guidance [.pdf] for industry, titled "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications." Comments to the draft guidance are due by December 30, 2009, and should be submitted according to the instructions in the Federal Register [.pdf] notice announcing the draft guidance.

Background

FDA gained authority to require REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85), effective March 2008. Pursuant to FDAAA, FDA may require applicants to submit a proposed REMS as part of a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) where the Agency deems it necessary to take additional steps to ensure that the product's benefits outweigh its risks. FDA also has the authority to require holders of approved applications to submit a proposed REMS if new safety information becomes available and FDA determines that a REMS is necessary.

Trends

During 2009, FDA has required an increasing number of REMS, already approving 32 this year compared to just 24 approvals from April through December of 2008. REMS must include an assessment timetable and may include any combination of the following: a Medication Guide, patient package insert, a communication plan for health care providers if the plan may support implementation of an element of the strategy, and elements to ensure safe use. The REMS timetable, which is mandated by statute, requires that assessments be conducted eighteen months, three years, and seven years after the REMS is first approved (or at a frequency specified in the strategy). While REMS approved in 2008 and in the early part of 2009 often have included only a Medication Guide, a recent trend appears to show that FDA is increasingly requiring that REMS include a communication plan, elements to ensure safe use, or an implementation system in addition to the Medication Guide. Moreover, with the announcement of a class-wide REMS for opioid products last May, and a *de facto* class-wide REMS for tumor necrosis factor (TNF) alpha blockers, FDA may be moving toward broader application of its REMS authority.

Draft Guidance

This draft guidance is the first that FDA has issued on REMS and provides FDA's current thinking on the format and content of a proposed REMS, including REMS supporting documentation. The draft guidance, for example, provides suggestions on how the information should be presented, what information should be included, and links to additional FDA website resources. In addition, Attachment A of the draft guidance provides a REMS exemplar for a fictitious drug. The draft guidance also discusses the content of REMS assessments and how proposed modifications of approved REMS should be submitted. This is critical for sponsors of drugs subject to the earliest REMS required in 2008, which should be scheduled for the mandatory eighteen month review this year. The draft guidance could provide helpful hints to these companies as they begin the unchartered REMS assessment process with FDA.

The draft guidance also provides some direction regarding how to communicate about a REMS with FDA based on which Center is regulating the product. For example, in the Center for Drug Evaluation and Research (CDER), the primary contact person for a proposed REMS is the regulatory project manager in the Office of New Drugs (OND) review division assigned to the specific product under an NDA or BLA. In the Center for Biologics Evaluation and Research (CBER), the primary contact for proposed REMS is the regulatory project manager in the product office.

Conclusion

Industry has been pressing FDA for months to offer guidance on REMS, which to date have been developed on a case-by-case basis between the agency and sponsor. The agency has now delivered, and, according to the press release accompanying the draft guidance, this guidance will not be the last on REMS. Stakeholders should carefully review the draft publication and offer constructive comments to the agency to facilitate more transparency in the REMS process and begin a productive dialogue. Ideally, this draft guidance will provide industry with the information it needs to not only develop REMS that effectively communicate risks and benefits to patients, but also to pass FDA scrutiny when subsequently assessed at the required intervals following initial REMS approval.