

Implementation of the FDA Amendments Act of 2007: FDA Draft Guidance on Postmarketing Studies and Clinical Trials

July 21, 2009

On July 15, the U.S. Food and Drug Administration (FDA) released a Draft Guidance for Industry titled “Postmarketing Studies and Clinical Trials—Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act.” The draft guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>.

Introduction

FDA is continuing its implementation of legislation passed almost two years ago. The Food and Drug Administration Amendments Act of 2007 (FDAAA) was signed into law by President Bush on September 27, 2007. Title IX, section 901 of FDAAA (Public Law 110–85) amended the Federal Food, Drug, and Cosmetic Act (the Act) by adding new section 505(o) (21 U.S.C. § 355(o)). Section 505(o) of the Act authorizes FDA to require certain postmarketing studies or clinical trials for prescription drug and biological products approved under section 505(b) of the Act or section 351 of the Public Health Service Act (PHS) (42 U.S.C. § 262). The Draft Guidance represents the FDA’s current thinking on the implementation of section 505(o) of the Act on postmarketing studies and clinical trials, but may be refined in response to public comments.

The Draft Guidance describes which types of postmarketing studies and clinical trials will generally be required (postmarketing requirements (PMRs)) under section 505(o) of the Act, and which types will be agreed-upon commitments because they do not meet the statutory criteria for required studies and trials (postmarketing commitments (PMCs)).

The Draft Guidance does not apply to nonprescription drugs approved under a New Drug Application (NDA) or generic drugs approved under section 505(j) of the Act.

Background

Past Practice. In the past, FDA has used the term “PMC” to refer to studies (including clinical trials) conducted by an applicant after FDA has approved a drug for marketing or licensing. These studies were intended to further refine the safety, efficacy, or optimal use of a product, or to ensure consistency and reliability of product quality. These PMCs were either agreed upon by FDA and the applicant or, in

certain circumstances, required by FDA. Prior to the passage of FDAAA, FDA required PMCs in the following situations:

- Subpart H and Subpart E accelerated approvals for products approved under section 505(b) of the Act or section 351 of the PHS Act, respectively, which require postmarketing studies to demonstrate clinical benefit (21 C.F.R. § 314.510 and § 601.41)
- Deferred pediatric studies, where studies are required under the Pediatric Research Equity Act (PREA) (21 C.F.R. § 314.55(b) and § 601.27(b))
- Animal Efficacy Rule approvals, where studies to demonstrate safety and efficacy in humans are required at the time of use (21 C.F.R. § 314.610(b)(1) and § 601.91(b)(1))

New FDAAA Authority and Requirements. Section 505(o)(3)(B) of the Act states that postmarketing studies and clinical trials may be required for one of the following three purposes:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

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Postmarketing Requirements (PMRs). PMRs under FDAAA generally would include, but not be limited to, the following:

- **Observational pharmacoepidemiologic studies** designed to assess a serious risk attributed to a drug exposure or to quantify risk or evaluate factors that affect the risk of serious toxicity, such as drug dose, timing of exposure, or patient characteristics.
- **Clinical trials with a primary safety endpoint**, evaluated with prespecified assessments. While efficacy may be evaluated, the primary goal of the PMR would be to evaluate safety.
- **Safety studies in animals** investigating specific end-organ toxicities, including but not limited to carcinogenicity and reproductive toxicity studies.
- **In vitro laboratory safety studies** designed, for example, to evaluate the potential and risks of off-target metabolite binding or drug resistance, to evaluate the risk of cross-contamination between products that could result from sharing product-contacting equipment and parts, or to validate an immunogenicity assay for a drug or biological product.
- **Studies or clinical trials to evaluate the pharmacokinetics of the drug** in the labeled population or in a subpopulation at potential risk for high drug exposures that could lead to toxicity.
- **Studies or clinical trials designed to evaluate drug interactions or bioavailability** when there are scientific data that indicate the potential for a serious safety risk.

Postmarketing Commitments. Generally, the following types of studies or clinical trials would not meet the statutory purposes for PMRs, but might be considered for agreed-upon PMCs:

- Drug and biologic quality studies, including manufacturing, stability, and immunogenicity studies, that do not have a safety endpoint, such as studies designed to:
 - Develop an optical rotation test, collect data on commercial batches, and use the data to update drug substance specification standards
 - Evaluate immune response to concomitant vaccination(s) that are a part of routine U.S. immunization practice
- Pharmacoepidemiologic studies designed to examine the natural history of a disease or to estimate background rates for adverse events, including vaccine surveillance and observational studies.
- Clinical trials in which the primary endpoint is related to further defining efficacy, designed to:
 - Evaluate efficacy using a withdrawal design
 - Evaluate long-term effectiveness or duration of response

Reporting. In general, FDA will interpret the periodic reporting requirement for PMRs, PMCs, and other studies and clinical trials independently conducted (section 505(o)(3)(E)(ii) of the Act) to be the annual reports required under 21 C.F.R. §§ 314.80, 314.81, and 601.70, unless otherwise stated by FDA. Therefore, applicants will be able to report both PMRs and PMCs at the same time and use the format recommended in the Guidance on the Status of PMCs, as long as the required elements of the PMR information described in the Draft Guidance are provided in the report. FDA plans to update the Guidance on the Status of PMCs (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>) to reflect the FDAAA-related changes.

In addition, section 505-1(g)(3) of the Act (21 U.S.C. § 355-1(g)(3)(B) and (C)) requires that the Risk Evaluation and Mitigation Strategy (REMS) assessments include the status of any postapproval studies and clinical trials required under section 505(o) and those that are otherwise undertaken to investigate a safety issue. Applicants can satisfy these requirements in their REMS assessments by referring to relevant information included in the most recent annual report required under section 506B of the Act and 21 C.F.R. § 314.81(b)(2)(vii) or 21 C.F.R. § 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS provisions in section 505-1(g) could result in enforcement action.

Implications

FDAAA, primarily Title IX, provides FDA with additional authorities, resources, and requirements with regard to both pre- and postmarketing drug safety. The statute contains important new authorities to require postmarketing studies and clinical trials, safety labeling changes, and REMS. FDAAA requires increased activities for active postmarketing risk identification and analysis. We recommend that applicants consider issues for postmarketing studies and clinical trials during product development prior to discussions of product approval to avoid last-minute negotiations concerning such trials, and ensure that company management understands that, under the new authority, FDA will take action for failure to comply in good faith with timelines. The applicant may appeal a requirement to conduct a postmarketing study or clinical trial using the usual dispute resolution procedures, but this will delay product approval.

An applicant's failure to comply with the timetable, periodic report submissions, and other requirements of section 505(o) of the Act will be considered a violation unless the applicant demonstrates good cause for the noncompliance. Under section 505(o)(3)(E)(ii) of the Act, FDA will determine what constitutes

good cause. Enforcement action for a violation of section 505(o)(3) may result in unapproved drug and/or misbranding charges and may be subject to civil monetary penalties as described in the Draft Guidance.

The new safety authorities in Title IX, Subtitle A of FDAAA took effect on March 25, 2008. Since then, FDA has issued more than 20 letters for drugs and biologics requiring postmarketing studies or clinical trials to address safety issues as mandated by section 505(o)(3). In the past, these kinds of studies would have been undertaken voluntarily, as postmarketing commitments; now they are required, and the established timeframes for the conduct of the study are enforceable. In addition, companies need to remember that FDAAA requires timely registration and posting of the results of these clinical trials in the www.clinicaltrials.gov database.

The implementation of section 505(o) of the Act is likely to result in increased costs of drug development due to increased postapproval spending, heavier postmarketing commitment burdens, increased requirements for safety assessment and reporting, and increased attention from FDA with respect to drug safety, postmarketing research, and eliminating the backlog of applicants' postmarketing commitments. We recommend that companies refine surveillance of available safety information, including adverse events from preapproval clinical trials, for potential safety signals, to anticipate the FDA's identification of a potential serious risk.

Submitting Comments on the Draft Guidance to FDA

Interested persons may submit written comments to the Division of Dockets Management (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, or electronic comments to <http://www.regulations.gov>.

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