
Guidance for Industry
Postmarketing Studies and
Clinical Trials —
Implementation of
Section 505(o)(3) of the
Federal Food, Drug, and
Cosmetic Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2011
Drug Safety

Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

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Guidance for Industry¹

Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides information on the implementation of new section 505(o) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(o)), added by section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 505(o)(3) authorizes FDA to require certain postmarketing studies and clinical trials² for prescription drugs approved under section 505 of the Act and biological products approved under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262).³ This guidance provides information about the requirements for postmarketing studies and clinical trials under section 505(o)(3) of the Act. The guidance also describes the types of postmarketing studies and clinical trials that:

- will generally be required under the new legislation (postmarketing requirements (PMRs)) and

¹ This guidance has been prepared by the FDAAA Title IX Working Group, comprising staff from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² FDAAA makes a new distinction between “study” and “clinical trial.” Previous laws, regulations, and practice have generally used the terms *studies* and *trials* interchangeably. For example, section 506B of the Act (21 U.S.C. 356b) uses “studies” to describe the postmarketing commitments (PMCs) that must be reported annually, including clinical trials. For purposes of implementing section 505(o)(3) of the Act, because FDAAA distinguishes between studies and clinical trials and section 505(o) provides criteria to determine which may be required (see section II.B of this guidance), we distinguish between studies and clinical trials for the purposes described in this document.

³ For the purposes of this guidance, all references to *drugs* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

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- will generally be agreed-upon commitments (postmarketing commitments (PMCs)) because they do not meet the new statutory criteria for required postmarketing studies and clinical trials.

Section 901 of FDAAA also created new sections 505-1 and 505(o)(4) of the Act, which authorize FDA, under certain circumstances, to require risk evaluation and mitigation strategies (REMS) to ensure that the benefits outweigh the risks of a drug and safety-related labeling changes (SLC) respectively.⁴ This guidance does not address REMS and SLC provisions. FDA wishes to clarify that PMRs, REMS, and SLCs are required under separate sections of the Act and while all are intended to address serious safety risks, they are separate provisions that have different goals and must meet separately defined statutory criteria. REMS are not a special type of PMR, nor are PMRs elements of a REMS.⁵

This guidance does not apply to nonprescription drugs approved under a new drug application (NDA), nor does it apply to generic drugs approved under section 505(j) of the Act. Section 505(o) of the Act applies only to prescription drugs approved under section 505(b) of the Act and biological products approved under section 351 of the PHS Act. See 505(o)(2)(B).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On September 27, 2007, the President signed FDAAA (Public Law 110-85) into law. Section 901 of Title IX of FDAAA amended the Act by adding new section 505(o). Section 505(o)(3) authorizes FDA to require certain postmarketing studies and clinical trials for prescription drugs approved under section 505(b) of the Act and biological products approved under section 351 of the PHS Act.

A. Past Practice

In the past, FDA has used the term *postmarketing commitment* (PMC) to refer to certain studies (including clinical trials), conducted by an applicant after FDA has approved a drug for marketing or licensing, that 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 generally

⁴ See the guidance for industry on *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.

⁵ See section V.D of this document for information on the requirement for REMS assessments to include information about the status of PMRs, PMCs, and studies and/or trials otherwise undertaken by the applicant to investigate a safety issue.

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agreed upon by FDA and the applicant. Prior to the passage of FDAAA, FDA required postmarketing studies or clinical trials only in the situations described below:

- Subpart H and subpart E accelerated approvals for products approved under 505(b) of the Act or section 351 of the PHS Act, respectively, which require postmarketing studies to demonstrate clinical benefit (21 CFR 314.510 and 601.41, respectively);
- Deferred pediatric studies, where studies are required under section 505B of the Act (21 CFR 314.55(b) and 601.27(b));⁶ and
- Subpart I and subpart H Animal Efficacy Rule approvals, where studies to demonstrate safety and efficacy in humans are required at the time of use (21 CFR 314.610(b)(1) and 601.91(b)(1), respectively).⁷

Section 130(a) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) amended the Act by adding a new provision requiring reports of certain postmarketing studies for human drug and biological products (section 506B of the Act (21 U.S.C. 356b)). Section 506B of the Act provides FDA with additional authority to monitor the progress of a PMC by requiring the applicant to submit a report annually providing information on the status of the PMC, which was defined to include agreed-upon commitments and required studies (including clinical trials).⁸ This report must also include the reasons, if any, for failure to complete the commitment. This provision is implemented at 21 CFR 314.81(b)(2)(vii) and 601.70.⁹ Under section 506B(b) and (c), FDA is required to track these PMCs and report on them annually in the *Federal Register*.¹⁰

B. New FDAAA Authority and Requirements

⁶ See the FDA guidance for industry on *How to Comply with the Pediatric Research Equity Act*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁷ See the FDA guidance for industry on *Animal Models—Essential Elements to Address Efficacy Under the Animal Rule*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁸ See the guidance for industry on *Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (guidance on the status of PMCs), available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁹ In addition, new drug application (NDA) applicants are required by 21 CFR 314.81(b)(2)(viii) to report annually to FDA on postmarketing studies or trials that are not 506B studies or trials. Such studies or trials are not required, and they include chemistry, manufacturing, and controls (CMC) studies that applicants have agreed with FDA to conduct (CMC commitments), and all product stability studies that applicants have agreed with FDA to conduct (stability studies). The reporting requirement at 21 CFR 314.81(b)(2)(viii) also includes “any postmarketing study not included under [§ 314.81](b)(2)(vii) . . . that is being performed by, or on behalf of, the applicant.” Reports on the status of these types of studies are not reports required under section 506B.

¹⁰ Available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>.

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1. FDA May Require Applicants to Conduct Studies and Clinical Trials

Section 505(o)(3) of the Act authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of *new safety information*.¹¹ Section 505-1(b)(3) of the Act defines new safety information to include data about a serious risk, or an unexpected serious risk associated with use of the drug (see Appendix A for the complete definition). Even if a serious risk is known at the time of approval of the drug, more may be learned after approval about its frequency or severity that can be considered new safety information.

In some cases, FDA may be concerned about a risk and believe that it is serious, but may not know enough about the risk to determine how to address the risk in labeling and what information would be appropriate to include. In such a case, FDA can require a postmarketing study or clinical trial to obtain more information. See purposes set forth in 505(o)(3)(A) below.

If there is information on chemically-related or pharmacologically-related drugs, FDA may consider this drug class safety information when requiring a study or clinical trial. See 505(o)(3)(A).

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

- 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

For the purposes of implementing section 901 of FDAAA,¹² clinical trials and studies are defined as follows:

- ***Clinical trials*** are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects.
- ***Studies*** are all other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

Clinical trials are one type of clinical investigation, as defined at 21 CFR 312.3(b). For the purposes of this guidance, FDA has separately defined these terms as listed above because statutory provisions below from section 505(o)(3) of the Act differentiate between studies and clinical trials.

¹¹ Defined at section 505-1(b)(3) of the Act (see Appendix A, Glossary).

¹² These definitions of postmarketing clinical trial and study do not affect whether the trials or studies are subject to the requirements of Title VIII of FDAAA (Clinical Trial Databases) and section 402(j) of the PHS Act (42 U.S.C. 282(j)).

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STATUTORY PROVISIONS

Under section 505(o)(3)(D)(i), before requiring a *postmarketing study*, FDA must find that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) of the Act will not be sufficient to meet the purposes described in section 505(o)(3)(B).

Under section 505(o)(3)(D)(ii), before requiring a *postmarketing clinical trial*, FDA must find that a postmarketing study will not be sufficient to meet the purposes described in section 505(o)(3)(B).

2. *Applicants Are Required to Report on the Status of Studies and Clinical Trials*

The applicant is required to provide certain information to FDA with regard to required postmarketing studies and clinical trials (section 505(o)(3)(E)(ii)). Under section 505(o)(3)(E)(ii), this information must include:

- For all required postmarketing studies and clinical trials, a timetable for completion
 - A *timetable for completion* is a set of milestone dates by which we measure progress of studies and clinical trials and compliance with requirements. These goal dates generally include, but are not limited to, final protocol submission date, study or clinical trial completion date, and final report submission date. FDAAA does not include provisions to amend or change milestone dates for purposes of reporting as required under 21 CFR 314.81(b)(2)(vii)(a)(8)(ii-iii) and 21 CFR 601.70(b)(8)(ii-iii). Therefore, status reporting under these regulations will remain based on the *original* schedule.
- For each study required under section 505(o)(3), periodic reports on the status of the study, including whether any difficulties in completing the study have been encountered
- For each clinical trial required under section 505(o)(3), periodic reports on the status of the clinical trial, including:
 - whether enrollment has begun,
 - the number of participants enrolled,
 - the expected completion date,
 - whether any difficulties completing the clinical trial have been encountered, and
 - registration information with respect to the clinical trial under section 402(j) of the PHS Act (42 U.S.C. 282(j))

In addition, FDAAA requires that applicants report on each study and clinical trial “otherwise undertaken by the applicant to investigate a safety issue” (see section 505(o)(3)(E)(ii)). Reports on these studies and clinical trials would previously have been required under 21 CFR 314.81(b)(2)(viii).

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III. IMPLEMENTATION OF POSTMARKETING STUDY AND CLINICAL TRIAL REQUIREMENTS UNDER FDAAA¹³

Under section 505(o)(3) of the Act, FDA will require applicants to conduct a postmarketing study or studies or clinical trial(s) when the following conditions are met:

1. When the decision to require a postmarketing study or clinical trial is based on scientific data deemed appropriate by FDA, including information regarding chemically-related or pharmacologically-related drugs; and
2. When FDA has found —
 - a. before requiring a postmarketing study, that adverse event reporting under section 505(k)(1) of the Act and the new pharmacovigilance system that will be established under section 505(k)(3) will not be sufficient to meet the purposes described in condition 3 below; and
 - b. before requiring a postmarketing clinical trial, that a postmarketing study will not be sufficient to meet the purposes in condition 3 below; and
3. When the purposes of the study or clinical trial, as described in section 505(o)(3)(B), are one or more of the following:
 - 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

When these conditions are met, the Agency intends to require the study or clinical trial as a *postmarketing requirement* (PMR).

We believe that the authority to require a responsible person to conduct a postapproval study or studies or clinical trial(s) of the drug includes the authority for FDA to describe the study or trial to be conducted, including how the study or trial is to be done and the population and indication. In other words, we can require a study or clinical trial that is well-designed and adequate to address the serious safety concern.

Examples of studies or clinical trials that meet criteria for PMRs are provided later in this document, and definitions of new safety information and serious risk are included in the Glossary at the end of this guidance document. The new safety information that prompts the postmarketing study or clinical trial after approval of a drug product will be described in the Agency's letter to applicants notifying them of the requirement.

¹³ Applicants conducting postmarketing studies and clinical trials must continue to comply with 21 CFR part 312 and 21 CFR part 58 when applicable, and Health and Human Services (HHS) and FDA human subject protection regulations at 45 CFR part 46 and 21 CFR parts 50 and 56 when applicable.

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The purposes outlined in section 505(o)(3)(B) are all related to drug safety. Although almost any study or clinical trial might be broadly construed to evaluate safety, FDA does not intend to consider all postmarketing studies and clinical trials as PMRs. We will generally require PMRs for all studies and clinical trials with purposes that meet the criteria for assessing or identifying a “serious risk” as described above. FDA also recognizes that many postmarketing studies and trials agreed upon as PMCs before FDAAA was enacted meet current standards for required safety studies and clinical trials under FDAAA. However, FDA does not intend to convert these PMCs to PMRs, unless new safety information relevant to a delayed PMC emerges.

Since FDAAA, the terms *PMR* and *PMC* are used as follows:

- The term *postmarketing requirement* or *PMR* is used to describe **all** required postmarketing studies or clinical trials, including those required under FDAAA and those required under subpart H of 21 CFR part 314, subpart E of 21 CFR part 601, the Pediatric Research Equity Act, and the Animal Efficacy Rule.
- The term *postmarketing commitment* or *PMC* is used to describe studies and clinical trials that applicants have agreed to conduct, but that will generally not be considered as meeting the statutory purposes in 505(o)(3)(B) and so will not be required.

Appendix B summarizes these authorities.

Described below in section III.A are the categories of postmarketing studies and clinical trials that will generally be considered as meeting the conditions described above for PMRs. Section III.B outlines the categories of studies and clinical trials that will generally not be required by statute or regulation, but may be PMCs.

A. Examples of Postmarketing Requirements (PMRs) Under Section 505(o)

PMRs under FDAAA generally would include, but not be limited to, the following:

- Observational pharmacoepidemiologic studies are generally studies designed to assess a serious risk associated with 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. To facilitate interpretation of the findings, the studies should always have a protocol, should include a control group, and should test prespecified hypotheses. However, control groups may be omitted when there is a scientifically valid reason to exclude controls. For a solely descriptive study, instead of a prespecified hypothesis, the protocol for a descriptive study may include clearly stated objectives for describing the safety issue, including a defined upper bound for detectable risk, if applicable. Data sources for observational studies could include administrative health care claims data, electronic medical records, registries, prospectively collected observational data, or other sources of observational information.
 - Registries may be designed with different goals.
 - Registries established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required as part

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of a REMS under section 505-1(f)(3)(F). When part of a REMS, they are an element necessary for the safe use of the drug, and are not designed as a study with completion dates. These types of registries would not be required as a PMR and are not described further in this guidance.

- A drug may be approved with a requirement for a registry that will collect data to be analyzed in a study required as a PMR (under section 505(o)(3)), outside of a REMS (section 505-1(f)(3)(F)). When a pharmacoepidemiologic study using registry data meets the statutory criteria for a PMR described above in section III, the registry and the study will be required as a PMR.
- A sponsor may voluntarily create a registry to serve as a repository for clinical data, such as an outcomes registry. Such a registry is not required as part of a PMR (section 505(o)(3)). However, if FDA becomes aware of new safety information in the post approval setting, the sponsor could be required to conduct a PMR study, which may utilize the registry data.

Examples of observational studies include pharmacoepidemiologic studies designed to:

- Estimate the risk of a serious adverse event or toxicity associated with use of a drug
 - Provide estimates of absolute risk (e.g., incidence rates) for a serious adverse event or toxicity
 - Obtain long-term clinical outcome data, including information about potentially rare serious adverse events, in patients taking the drug compared to patients not exposed to the drug
 - Identify risk factors (e.g., patient characteristics, duration of drug use) associated with the occurrence of adverse events among patients exposed to specified drugs.
 - Compare pregnancy incidence, pregnancy outcomes, and/or child outcomes after patient drug exposure compared to patients who did not receive the drug
- Meta-analyses may be designed to evaluate a safety endpoint by statistical analysis of data from completed studies or clinical trials. A meta-analysis should use a prospectively designed study protocol and analysis plan with a comprehensive selection of relevant studies or clinical trials and appropriate statistical methodology.
 - Perform a meta-analysis of the occurrence of all-cause mortality, cardiovascular death, and cancer incidence and identify potential predictive factors in patients treated with the drug compared to control therapies in all completed randomized clinical trials that include the drug
 - Clinical trials with a safety endpoint evaluated with prespecified assessments and adequately powered to analyze the serious risk identified by FDA under section 505(o)(3) would be considered PMRs. Although efficacy endpoints may also be evaluated, the trial should be

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powered to adequately assess the safety concern that gives rise to the requirement. Examples include *clinical trials* designed to:

- Evaluate the occurrence of asthma exacerbations associated with an irritative component of inhalation treatments for asthma in a controlled clinical trial, where the increased risk of drug-related exacerbation has the potential to offset the effectiveness of the inhaled drug
 - Determine the incidence of myocardial infarction in patients treated with the approved drug in a follow-on trial after approval, using the original randomized population
 - Evaluate differences in safety outcomes between patients withdrawn from treatment after some period of treatment and patients who remain on the treatment (randomized withdrawal trial)
 - Evaluate the potential for Q-T prolongation in a thorough Q-T clinical trial
 - Measure growth and neurocognitive function in pediatric patients treated chronically with the drug¹⁴
 - Evaluate safety in a particular racial or ethnic group or vulnerable population such as the immunocompromised¹⁴
 - Evaluate the safety of the drug in pregnant women¹⁴
 - Evaluate drug toxicity in patients with hepatic or renal impairment¹⁴
 - Evaluate long-term safety of cell and gene therapy products depending on the type of vector used and the inherent risk of integration
 - Evaluate the safety of a drug in patients with HIV-1 co-infected with hepatitis C or B¹⁴
- Safety studies in animals investigating specific end-organ toxicities, including, but not limited to carcinogenicity and reproductive toxicity studies. Although in most instances these studies are completed prior to marketing approval, they may be conducted postapproval for certain drugs — for example, products intended to treat serious and life-threatening diseases.¹⁵ If conducted postapproval, these studies would be required under 505(o). Examples include studies designed to:
 - Assess carcinogenic potential in appropriate species (e.g., mice and rats)
 - Assess the potential for reproductive toxicology in appropriate species (e.g., monkeys or rabbits)
 - Examples of in vitro laboratory safety studies that would qualify as PMRs would be studies designed to:

¹⁴ Patients are treated with the drug at a dose and schedule specified in the clinical trial protocol.

¹⁵ See the ICH S1A guidance for industry on *The Need for Long Term Rodent Carcinogenicity Studies of Pharmaceuticals*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065007.htm>.

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- Assess certain receptor affinities for any circulating or major metabolites, including conjugates, to evaluate the potential for off-target binding and resulting serious risk
 - Determine whether resistance to a drug has developed in those organisms specific to the labeled indication, resulting in increased serious risk
 - Define the mechanism of drug resistance for certain organisms
 - Assess the risk of cross-contamination between products that could result from sharing product-contacting equipment and parts
 - Validate the accuracy, precision, sensitivity, specificity, and robustness of an immunogenicity assay for a drug or biological product to assess an immunologic safety concern
- Pharmacokinetic studies or clinical trials that would be PMRs include those 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. Examples include studies or clinical trials designed to:
 - Determine the optimal dose for maintenance therapy in patients with chronic renal disease, a population at risk for drug accumulation
 - Study the pharmacokinetic profile in a rodent model of hepatic dysfunction in order to evaluate the potential for toxicity in patients with liver impairment
 - 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. Examples include studies or clinical trials to:
 - Assess in vitro whether products are p-glycoprotein substrates and therefore could lead to increased drug concentrations and toxicity
 - Assess potential interactions of an approved drug with a frequently concomitantly prescribed medication
 - Evaluate whether multiple doses of an approved drug alter the metabolism of a sensitive CYP2C9 substrate
 - Evaluate bioavailability of an oral drug in the presence of food

B. Examples of Postmarketing Commitments (PMCs) That Are Not Required Under Section 505(o)(3)

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 primary 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

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- 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 in a population not treated with the drug that is the subject of the marketing application.
- Studies and clinical trials conducted with vaccines, such as surveillance and observational pharmacoepidemiologic studies when data do not suggest a serious risk or signals of serious risk related to the use of the vaccine and when available data do not indicate the potential for serious risk, such as:
 - A surveillance study of cases of the infectious disease targeted by the approved vaccine occurring in vaccinated populations; conduct product-specific surveys and calculate product-specific rates of infectious disease within the monitored population
 - A clinical trial conducted with vaccines in which the objective is a further characterization of the safety profile and the primary endpoint is not related to a serious risk identified by FDA under section 505(o) of the Act
- Clinical trials in which the primary endpoint is related to further defining efficacy, designed to:
 - Evaluate long-term effectiveness or duration of response¹⁶
 - Evaluate efficacy using a withdrawal design
 - Evaluate efficacy in a subgroup

IV. PROCEDURES

As outlined in section X.B of the Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures, FY 2008-2012,¹⁷ FDA plans to inform the applicant of the planned target date for communication of feedback from the review division to the applicant regarding PMRs and PMCs in a letter sent within 14 days of the 60-day filing date of the marketing application. Generally, the designated planned target date will be no later than 1 month prior to the PDUFA goal date.

FDA plans to communicate a list of potential PMRs and PMCs, clearly delineated as to which are required and which may be agreed upon, to the applicant near the target date along with a brief rationale for why FDA thinks these studies and clinical trials are necessary. The list will also include a request for a proposed timetable for completion.

¹⁶ Not related to a subpart H requirement—efficacy trials that are not required as part of accelerated approval (AA). Clinical trials required under AA are PMRs.

¹⁷ Attachment to Letter to Chairman Dingell from Michael O. Leavitt, Secretary HHS, September 27, 2007, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm>.

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The applicant will have the opportunity to discuss the design and conduct of the PMRs and PMCs, as well as the overall goal, with the FDA review team. The applicant should provide prompt feedback and engage in discussion as needed with the FDA review team to facilitate completion of clearly written and well-designed PMRs and PMCs. The applicant should also provide a timetable for completion of the study or clinical trial for the PMRs and a schedule for milestone submissions and final reports for PMCs.¹⁸ For PMRs and PMCs, the first milestone is generally the “final protocol submission” date. “Final” implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. As described in section II.B.2 of this guidance, public status of PMRs and PMCs is based on the original schedule, so appropriate and realistic dates should be proposed.

The FDA review team will (1) review the potential study or clinical trial designs to make sure they will serve the purposes of the study or clinical trial and (2) assess whether the proposed timetable will be realistic and will provide for timely completion of the study or clinical trial.

FDAAA gives FDA the authority to require PMRs without prior agreement from the applicant. For PMCs, the applicant should submit a written agreement to conduct the PMCs. The PMRs and PMCs, and their milestones and dates, will be included in the action letter issued at the completion of the application review.

V. REPORTING

Except when otherwise provided, an applicant may satisfy its obligation to “periodically report” on the status of PMRs and other studies and clinical trials undertaken to investigate a safety issue by submitting the annual status reports required under 21 CFR 314.81 or 601.70 if the required elements of information about the status of the PMR information, set forth in section 505(o)(3)(E)(ii), are accurately and completely provided in that report. Therefore, applicants will be able to report on both PMRs and PMCs at the same time and use the format recommended in the guidance on the status of PMCs,¹⁹ as long as the applicant includes the required PMR status information, which is described below. On a case-by-case basis, a PMR may impose an additional obligation to “periodically report” at specified milestones.

A REMS assessment also must include information about the status of PMRs, PMCs, and studies and/or trials otherwise undertaken by the applicant to investigate a safety issue. See section 505-1(g)(3). This requirement is discussed below.

A. PMR Reports

¹⁸ Milestone dates are a series of goal dates (e.g., final protocol submission, study or clinical trial completion date, final report submission) by which we measure progress of studies and clinical trials and compliance with requirements.

¹⁹ The guidance on the status of PMCs will be updated to reflect FDAAA-related changes.

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For each PMR required under FDAAA, the applicant must periodically report on the status of the study or clinical trial (see section 505(o)(3)(E)(ii)). For clinical trials, the report must also include whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trials have been encountered, and registration information as required under section 402(j) of the PHS Act (see section 505(o)(3)(E)(ii)). We recognize that some of the information required for clinical trial reporting is also relevant to observational pharmacoepidemiologic studies, and FDA will interpret the requirement to include this information as applicable to all studies or clinical trials performed in humans. Registration information for clinical trials should include documentation that the PMR is registered in accordance with Title VIII of FDAAA.²⁰

B. PMC Reports

For each PMC under section 506B of the Act, applicants are required to report annually on the status of the studies or clinical trials (21 U.S.C. 356b(a); 21 CFR 314.81(b)(2)(vii) and 601.70(b)). The recommendations regarding compliance with section 506B may be found in the guidance on the status of PMCs.

C. Reports for Studies and Clinical Trials Otherwise Undertaken

For studies or clinical trials otherwise undertaken by the applicants to investigate a safety issue, the applicant must report to FDA under section 505(o)(3)(E)(ii) of the Act and 21 CFR 314.81(b)(2)(viii). These studies or clinical trials are neither required by FDA nor agreed upon between FDA and the applicant. They may include investigations initiated by an applicant for many reasons without prior discussion with or notification to FDA. These studies and clinical trials must be summarized in a section of the annual report (drugs) or annual status report (biologics).

D. Reports in REMS Assessments

In addition, section 505-1(g)(3) of the Act at paragraphs (B) and (C) (21 U.S.C. 355-1(g)(3)(B) and (C)) requires that risk evaluation and mitigation strategy (REMS) assessments include the status of postapproval studies and clinical trials required under section 505(o) and those that are otherwise undertaken to investigate a safety issue. PMRs are not part of REMS and are not submitted as part of the REMS, but must be described in REMS assessments. 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 CFR 314.81(b)(2)(vii) or 21 CFR 601.70, and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in section 505-1(g) could result in enforcement action.

²⁰ See FDA's guidance on *Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007*, available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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E. Summary

Applicants may generally report on PMRs, PMCs, and studies or clinical trials undertaken by the applicant to investigate a safety issue in periodic reports (e.g., annually) that are already required by our regulations. On a case-by-case basis, a PMR may impose an additional obligation to “periodically report” at specified milestones. In addition, although most PMRs and PMCs will be conducted under the IND for a drug, annual reports are required under the NDA/BLA. When multiple related applications exist (e.g., several formulations of the same drug with the same applicant), unified reporting, consistent with past practice, may be considered. An applicant who proposes unified reporting should discuss the proposal with the review division. REMS assessments, submitted under the NDA/BLA, are required under separate schedules. While the REMS assessments may reference the annual report for the required PMR reporting, the annual report does not replace the REMS assessment.

VI. DISPUTE RESOLUTION

The applicant may appeal a requirement to conduct a postmarketing study or clinical trial using the usual dispute resolution procedures (see the guidance for industry on *Formal Dispute Resolution: Appeals Above the Division Level*)²¹ (see section 505(o)(3)(F) of the Act).

VII. ENFORCEMENT OF REQUIREMENTS FOR POSTMARKETING STUDIES AND CLINICAL TRIALS

The new amendments to the Act give FDA authority to enforce the section 505(o)(3)(E)(ii) requirements for postmarketing studies and clinical trials.²² An applicant’s failure to comply with the timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) 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 is authorized to determine what constitutes good cause. In addition, under section 505(p)(2), failure to conduct a postmarketing study or trial required under subparts H and E (21 CFR 314.510 and 601.41) may result in enforcement action.

Enforcement action could include one or more of the following:

- Charges under section 505 of the Act. A responsible person²³ may not introduce or deliver into interstate commerce the drug involved if the applicant is in violation of section 505(o)

²¹ Available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

²² FDA has the authority to review records upon inspection of postmarketing studies and clinical trials, including underlying data and source documents (see section 505(k) of the Act).

²³ Defined at section 505(o)(2)(A) of the Act.

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(postmarketing study and clinical trial requirements) (see section 505(o)(1) of the Act) or 505(p)(2) (certain postmarketing studies).

- **Misbranding charges.** A drug is misbranded under section 502(z) of the Act (21 U.S.C. 332(z)) if the applicant for that drug violates postmarketing study or clinical trial requirements, including those outlined in section V above.
- **Civil monetary penalties.** Under section 303(f)(4)(A) of the Act (21 U.S.C. 333(f)(4)(A)), an applicant that violates postmarketing study or clinical trial requirements may be subject to civil monetary penalties of up to \$250,000 per violation, but no more than \$1 million for all violations adjudicated in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the applicant of the violation. The penalties double for the following 30-day period and continue to double for subsequent 30-day periods, up to \$1 million per period and \$10 million for all violations adjudicated in a single proceeding. In determining the amount of a civil penalty, FDA will consider the applicant's efforts to correct the violation (see section 303(f)(4)(B) of the Act).

GLOSSARY

The following definitions of terms are from section 505-1(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1(b)).

Adverse drug experience includes an adverse event occurring in the course of the use of the drug in professional practice.

New safety information with respect to a drug, means information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by the Secretary (of Health and Human Services) about —

(A) a serious risk or unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

Serious adverse drug experience is an adverse drug experience that —

(A) results in —

(i) death;

(ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);

(iii) inpatient hospitalization or prolongation of existing hospitalization;

(iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

(v) a congenital anomaly or birth defect; or

(B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

Serious risk means a risk of a serious adverse drug experience.

Signal of a serious risk means information related to a serious adverse drug experience associated with use of a drug and derived from —

(A) a clinical trial;

(B) adverse event reports;

(C) a postapproval study, including a study under section 505(o)(3);

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- (D) peer-reviewed biomedical literature;
- (E) data derived from the postmarket risk identification and analysis system under section 505(k)(4);
- (F) other scientific data deemed appropriate by the Secretary.

Unexpected serious risk means a serious adverse drug experience that is not listed in the labeling of a drug, or that may be symptomatically or pathophysiologically related to an adverse drug experience identified in the labeling, but differs because of greater severity, specificity, or prevalence.

FDA interprets these definitions to include safety information related to a class effect, not apparently limited to a single member of the class for structural, mechanistic, or other reasons.

PMR AND PMC AUTHORITIES

Postmarketing Requirement Authorities	Postmarketing Commitment Authority
Pediatric Research under Section 505B of the Act: <ul style="list-style-type: none"> • 21 CFR 314.55(b) (drugs) • 21 CFR 601.27(b) (biologics) 	Agreed Upon Postmarketing Studies and Clinical Trials: <ul style="list-style-type: none"> • 21 CFR 312.85
Accelerated Approval regulations: <ul style="list-style-type: none"> • 21 CFR 314.510, Subpart H (drugs) • 21 CFR 601.41, Subpart E (biologics) 	
Animal Rule: <ul style="list-style-type: none"> • 21 CFR 314.610(b)(1), Subpart I (drugs) • 21 CFR 601.91(b)(1), Subpart H (biologics) • 	
FDAAA, Section 901: <ul style="list-style-type: none"> • Section 505(o)(3) of the FDCA 	