
Guidance for Industry

Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997

**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)**

**February 2006
Procedural**

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Guidance for Industry¹
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Implementation of Section 130 of the Food and Drug
Administration Modernization Act of 1997

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

The purpose of this guidance is to assist applicants in meeting the requirements of section 130 of the Food and Drug Administration Modernization Act of 1997. This guidance provides recommendations on procedures, content, and format for submitting a postmarketing study commitment status report for an approved human drug or licensed biological product. This guidance also describes the FDA's obligations to make certain information about postmarketing study commitments public, including the type of information that will be made public and the FDA's time frames for reviewing postmarketing study commitment final reports.

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

A. Legislative History of Postmarketing Study Commitment Status Reports

Section 130(a) of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), signed into law on November 21, 1997, added section 506B (Reports of

¹ This guidance has been prepared by the Postmarketing Study Commitments Working Group, which includes representatives from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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Postmarketing Studies) to the Federal Food, Drug, and Cosmetic Act (the “Act”) (21 U.S.C. 356b). Section 506B gives the FDA additional authority for monitoring the progress of postmarketing studies that drug and biologics applicants (“you”) have agreed to or are required to conduct. On October 30, 2000, the FDA issued final regulations implementing that law (65 FR 64607). The regulations went into effect on April 30, 2001 (66 FR 10815), and FDA issued a draft guidance related to the rule in April 2001. This final guidance complements the rule by describing in greater detail the content, format, and timing of the postmarketing study commitment reports required by section 506B. The guidance also discusses reporting of other postmarketing studies not subject to section 506B.

If you are required by the FDA, or if you have entered into an agreement with the FDA, to conduct a postmarketing study concerning clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology, you are required to provide the Agency with an annual report on the status of the study until the FDA notifies you, in writing, that the Agency concurs with your determination that the study commitment has been fulfilled or that the study either is no longer feasible or would no longer provide useful information. This annual report must address the progress of the study or the reasons for your failure to conduct the study (21 U.S.C. 356b(a); 21 CFR 314.81(b)(2)(vii) and 601.70(b)).

Section 506B also requires the FDA to make certain information available to the public about postmarketing study commitments, and your progress in completing those studies. More specifically, under section 506B(c), the FDA must develop and publish annually in the *Federal Register* a report on the status of postmarketing study commitments that you have agreed to or are required to conduct and for which annual status reports have been submitted (21 U.S.C. 356b(c)). Section 506B(b) indicates that any information necessary to identify you as the applicant of a study and establish the status of a study and the reasons, if any, for any failure to carry out the study, is considered to be public information (21 U.S.C. 356b(b)).

B. Regulations for Reporting Postmarketing Studies

The regulations implementing section 506B of the Act apply to both human drug products and licensed biological products (21 CFR 314.81(b)(2)(vii) and 601.70). These regulations are summarized as follows:

- Applicants are required to file postmarketing study commitment status reports (506B reports) for studies that the FDA has required an applicant to conduct or that an applicant has agreed, in writing, to conduct, provided that the study concerns a product’s clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (506B studies). Information from 506B reports will be included in the Agency’s annual *Federal Register* report and on the postmarketing study commitments Web site.²
- The regulations apply to 506B studies for all approved applications, with no exception for products that are not actively marketed.

² <http://www.fda.gov/cder/pmc>

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- The regulations apply only to approved human drug products and licensed biological products that meet the definition of *drug* under the Act. The regulations do not apply to biological products that meet the definition of *device* under the Act. Such biological devices may be subject to the device postmarket surveillance provisions in section 522 of the Act (21 U.S.C. 360I). The rule does not apply to new animal drugs.
- 21 CFR 314.81(b)(2) provides that new drug application (NDA) applicants will continue to report to the FDA on postmarketing studies that are not 506B studies under another section of the annual report requirements (21 CFR 314.81(b)(2)(viii)). These are studies conducted without a commitment to the FDA (voluntary studies); chemistry, manufacturing, and controls study commitments that you have agreed with the FDA to conduct (CMC commitments); and all product stability studies (stability studies). Reports on the status of voluntary studies, CMC commitments, and stability studies are not 506B reports. Accordingly, the 506B provisions concerning public disclosure, including disclosure on the FDA's Web site and in the annual *Federal Register* reports, are not applicable to these studies. Applicants for licensed biological products are not required to submit reports of voluntary studies and CMC commitments to the FDA under 21 CFR 601.70. If submitted voluntarily to the FDA, such reports would not be 506B reports.

C. Types of Postmarketing Studies and Reasons for Conducting Them

Applicants frequently perform studies after the FDA approves a product for marketing. The studies are used to gather additional information about product safety, efficacy, or optimal use. Postmarketing studies are also used to evaluate CMC issues, which are important for ensuring consistency and reliability of product quality.

Generally, a postmarketing study would be conducted in one of the following circumstances.

- The FDA can *require* you to conduct a postmarketing study in certain situations. For example, the FDA can require you to conduct studies to verify and describe clinical benefit for a drug or biological product approved in accordance with the accelerated approval provisions (21 U.S.C. 356(b)(2)(A); 21 CFR 314.510 and 601.41). For a drug or biological product approved on the basis of animal efficacy data because human efficacy studies are not ethical or feasible, an applicant must conduct studies when ethical and feasible to verify and describe clinical benefit and to assess the product's safety (21 CFR 314.610(b)(1) and 601.91(b)(1)). Section 2 of the Pediatric Research Equity Act of 2003 (PREA) authorized the FDA to require pediatric studies of marketed drugs that are not adequately labeled for children. These studies may be deferred if the drug is ready for approval in adults before pediatric studies are completed or because of concerns about the safety or effectiveness of the drug in pediatric populations (21 U.S.C. 355B(a); P.L. 108-155). The FDA may also issue an order or regulation requiring an applicant to provide a study report that is necessary and relevant to a determination concerning whether there is or may be grounds for revoking approval of an approved drug (21 U.S.C. 355(k)(1)). You must file 506B reports for all postmarketing study commitments that

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you are *required* to conduct provided that the study concerns a product's clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology.

- A postmarketing study might be conducted because you and the FDA *agree*, in writing, that one or more such study should be conducted. These agreements can be made at the time of approval or after the FDA grants marketing approval to your drug. If you and the FDA agree at the time of drug approval that a postmarketing study should be performed, the study will likely be used to provide additional information about product risks, benefits, and/or optimal use. If you and the FDA determine after approval of the drug that a postmarketing study should be performed, the study will generally be used to address a safety concern that has been identified during the post-approval use of the drug. You must file 506B reports for postmarketing study commitments that you *agreed*, in writing, to conduct provided that the study concerns a product's clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology, and provided that the study commitment is not a CMC commitment.
- Frequently, postmarketing CMC studies are conducted because applicants agree, in writing, to conduct such studies to ensure the consistency and reliability of product quality (e.g., strength, purity, and potency). CMC commitments are not subject to 506B's reporting requirements, although 21 CFR 314.81(b)(2)(viii) requires you to advise the FDA on the status of CMC commitments in another section of your annual report.
- Product stability studies are conducted to determine the appropriate expiration date for drug products (21 CFR 211.166). Product stability studies are not subject to 506B's reporting requirements, although 21 CFR 314.81(b)(2)(viii) requires you to advise the FDA on the status of all product stability studies in another section of your annual report.
- A voluntary study can be conducted on an applicant's *own initiative* for a variety of reasons, such as the evaluation of a new indication, a new delivery system for a drug, a new container or closure system, or a new formulation. Voluntary studies are not subject to 506B's reporting requirements, although 21 CFR 314.81(b)(2)(viii) requires you to advise the FDA on the status of voluntary studies in another section of your annual report.

D. Summary of the Final Rule that Implements Section 506B

1. Human Drug Products

The final rule amended 21 CFR 314.81(b)(2)(vii) to implement section 506B. Under this section, you must provide the FDA with annual 506B reports on each 506B study annually until we notify you, in writing, that the FDA concurs with your determination that the study commitment has been fulfilled, or that the study is either no longer feasible or would no longer provide useful information. This provision will apply in rare cases to the holder of an abbreviated new drug application (ANDA).

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Under 21 CFR 314.81(b)(2)(viii), the final rule requires you to provide the FDA with annual status reports on voluntary studies that are being performed by you or on your behalf, CMC commitments that you have agreed to perform, and for all stability studies.

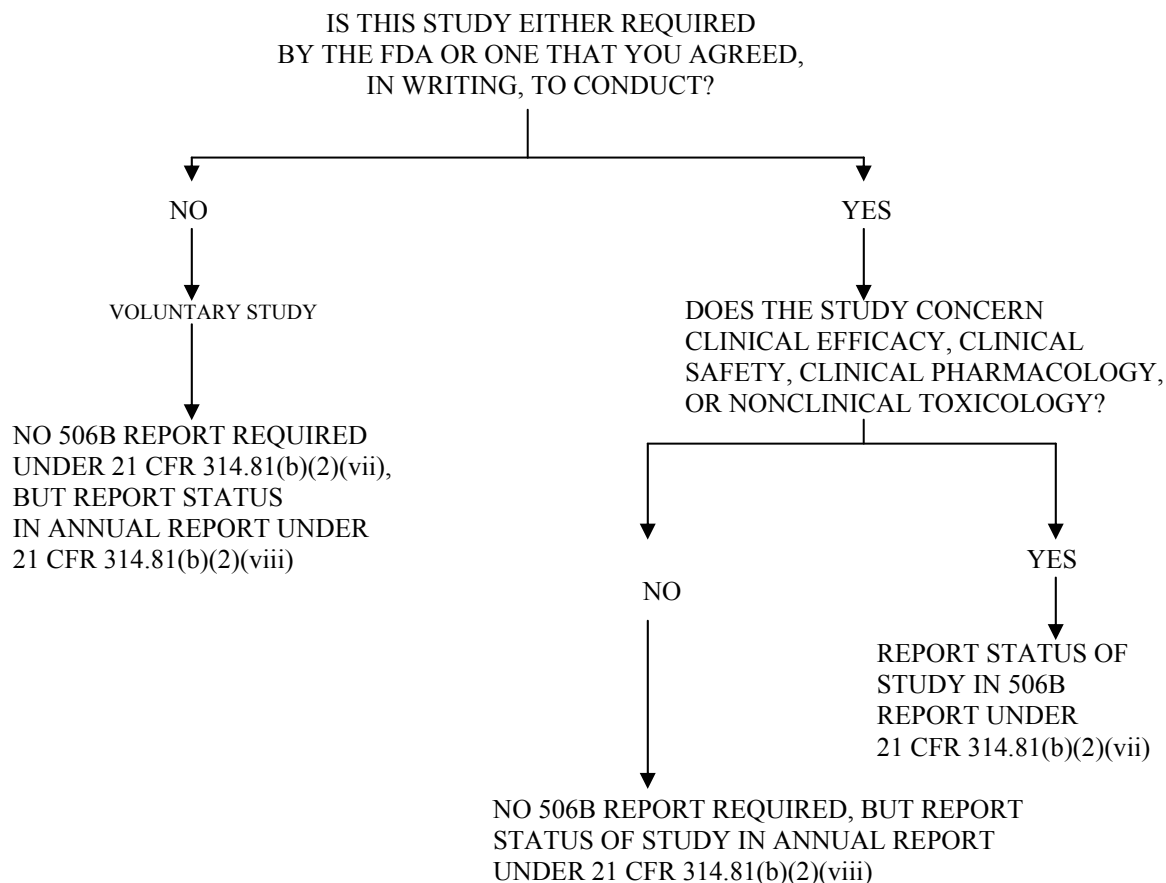
Under 21 CFR 314.81(b)(2)(ix), you may list any open regulatory business with the FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the Agency, a list of the Agency's unanswered correspondence with the applicant).

The FDA provides in its annual *Federal Register* report and on its Web site information submitted in annual status reports under 21 CFR 314.81(b)(2)(vii). The FDA does not disclose under the public disclosure provisions of 506B information about voluntary studies, CMC commitments, stability studies, or any open regulatory business submitted in NDA annual reports under 21 CFR 314.81(b)(2)(viii) or 314.81(b)(2)(ix).

A summary of the requirements for postmarketing study commitment status reports of human drug products, as stated in the rule, is depicted in the following flow chart.

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NDA/ANDA REPORTING REQUIREMENTS FOR POSTMARKETING STATUS REPORTS



2. *Licensed Biological Products*

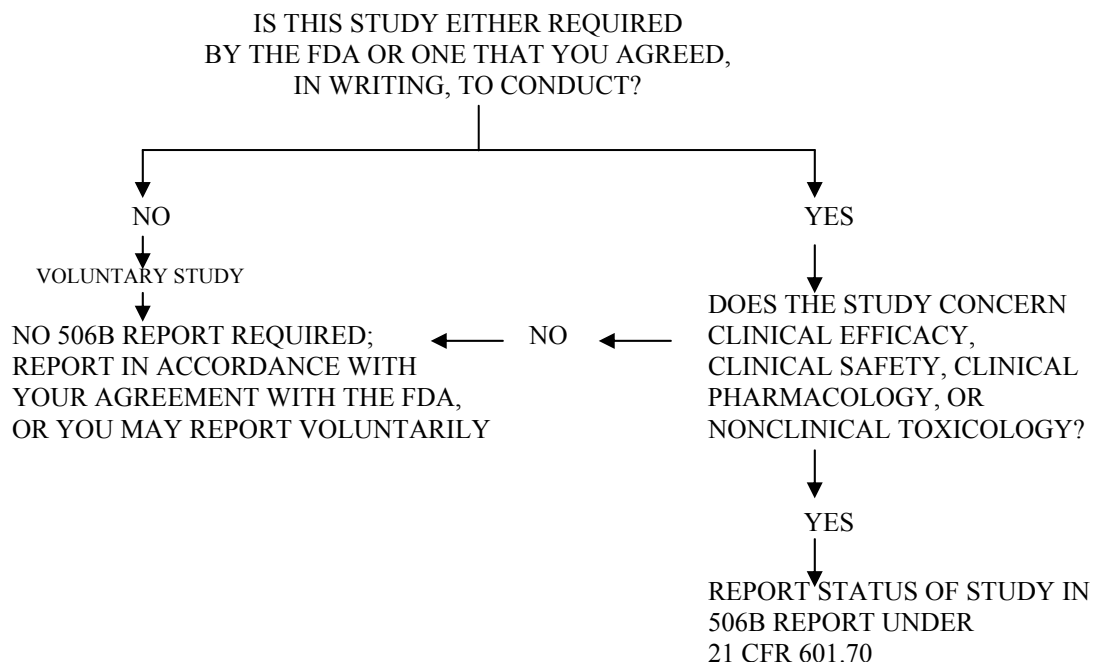
To implement section 506B of the Act, the final rule required annual 506B reports, and revised existing requirements for reports of postmarket pediatric studies to require 506B reports to be filed under 21 CFR 601.70.

Under new 21 CFR 601.70, you must provide the FDA with 506B reports on each 506B study annually until we notify you, in writing, that the FDA concurs with your determination that the study commitment has been fulfilled, or that the study is either no longer feasible or would no longer provide useful information. Status reports on voluntary studies, CMC commitments, and stability studies should not be reported under 21 CFR 601.70. The status of these studies should be reported according to your agreement, if any, with the FDA, and you may report them voluntarily.

A summary of the requirements for postmarketing study commitment status reports of licensed biological products, as stated in the rule, is depicted in the following flow chart.

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BLA REPORTING REQUIREMENTS FOR POSTMARKETING STATUS REPORTS



III. PROCEDURES CONCERNING POSTMARKETING STUDY COMMITMENTS

A. Submitting Postmarketing Study Commitment Protocols

The type of study and the agreements you reached with the Agency before product approval — or post-approval, in some cases — will influence when the protocol for a postmarketing study commitment should be submitted. The time frame for submitting the study protocol should be negotiated between you and the review division as a part of your commitment. However, it is generally expected that you will submit the protocol for required studies (e.g., accelerated approval clinical benefit studies, animal efficacy clinical benefit and safety studies) before approval of your application. The FDA intends to undertake timely review of the submitted protocol.

Protocols for clinical studies requiring an investigational new drug application (IND) should be submitted to the appropriate IND with a copy of the cover letter to the NDA, ANDA, or biologics license application (BLA). Protocols for studies not requiring an IND (e.g., toxicology or CMC studies) should be submitted to the NDA, ANDA, or BLA. If you have specific questions for the FDA regarding the protocol design, study conduct, study goals, and/or data analysis, you should include those focused questions as part of the cover letter in the submission. All submissions should be clearly labeled **Postmarketing Study Commitment Protocol**.

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B. Establishing a Study Schedule

For each 506B study, you must develop a schedule for completing that commitment (21 CFR 314.81(b)(2)(vii)(a)(7) and 601.70(b)(7)). Often, the study schedule is established at the time of approval and documented in the Agency's approval letter for the application, and you would report that schedule in your initial 506B report. Otherwise, you must establish that schedule in your initial 506B report. The study schedule included in your 506B report should provide, for each commitment, dates for submission of the study protocol to the FDA, dates for completion of patient accrual (or initiation of an animal study, if applicable), dates for completion of the study, dates for submission of the final study report to the FDA, and any additional dates, if the commitment specifies projected dates for any additional milestones or submissions.

Study schedules are sometimes developed with reference to the date that you and the FDA agree on the protocol (protocol agreement date). If you request and obtain FDA review of and agreement to a proposed study protocol, establish subsequent dates in your schedule with reference to the protocol agreement date. In most cases, you and the FDA will have concurred on a protocol before you are required to file your first annual postmarketing study commitment status report for that commitment, and you will be able to use actual dates for each entry in the schedule (e.g., Projected Final Study Report Submission Date: June 1, 2006). For instances when you and the FDA have not reached concurrence on a protocol before you file your first annual postmarketing study commitment status report (e.g., your annual report for a drug is due shortly after you entered into a commitment), you can describe your schedule dates by reference to a period of time from a protocol agreement date (e.g., *completion of patient accrual: 6 months after protocol agreement; completion of the study: 12 months after protocol agreement*).

If you choose not to request FDA review of and agreement to the study protocol, you should establish a schedule for study completion, including dates for completing all study milestones, without reference to a protocol agreement date. We note that if you proceed without Agency review of the study protocol, it is possible that, when the study is concluded, the FDA may not agree that the completed study satisfies your commitment.

You do not need to provide schedules for studies conducted on your own initiative (e.g., without a commitment to, or requirement by, the FDA).

C. Revising a Study Schedule

If it becomes necessary for any reason to revise the projected dates for study milestones, submit a revised study schedule, along with the reasons for the revision, in your next 506B report (21 CFR 314.81(b)(2)(vii)(a)(9) and 601.70(b)(9)). Although schedule revisions are sometimes necessary, we will use the *original* study schedule to determine the study progress and to designate its status as pending, ongoing, or delayed (21 CFR 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8)). If the schedule has been previously revised, you must include a copy of the original study schedule and the most recently revised schedule in your annual status report (21 CFR 314.81(b)(2)(vii)(a)(7),(9) and 601.70(b)(7),(9)) (see section IV).

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D. When to Submit Postmarketing Study Commitment Status Reports

You must submit 506B reports for both human drugs and biological products annually until we notify you, in writing, that the FDA concurs with your determination that the study commitment has been fulfilled, or that the study is either no longer feasible or would no longer provide useful information (21 CFR 314.81 (b)(2)(vii) and 601.70(b)) (see section III.G.). Your 506B report must be submitted to the FDA each year within 60 days of the anniversary of the FDA's approval of your NDA, ANDA, or BLA (21 CFR 314.81(b)(2) and 601.70(c)).

E. How to Submit Annual Postmarketing Study Commitment Status Reports

1. Human Drug Products

Your annual report should clearly distinguish 506B reports from reports on the status of voluntary studies, CMC commitments, and stability studies, with separate headings for each section. However, it is useful to list or cross-reference the CMC study commitments that you have agreed, in writing, to conduct and whose statuses are reported under 21 CFR 314.81(b)(2)(viii) in the "Status Reports of Postmarketing Study Commitments" section of the annual report. The cover letter should clearly identify the annual report submission as including an **Annual Status Report of Postmarketing Study Commitments**. The annual report must be accompanied by one copy of Form FDA-2252 (Transmittal of Annual Reports for Drugs and Biologics for Human Use) (21 CFR 314.81(b)(2)).

Two copies of your annual reports for human drug products must be sent to the review division responsible for reviewing the application (21 CFR 314.81(b)(2)). We encourage the electronic submission of annual reports, including 506B reports, submitted according to the electronic records requirements described under 21 CFR part 11.

2. Licensed Biological Products

The cover letter for annual 506B reports filed under 21 CFR 601.70 should clearly identify the submission as an **Annual Status Report of Postmarketing Study Commitments**. The annual report must be accompanied by one copy of Form FDA-2252 (Transmittal of Annual Reports for Drugs and Biologics for Human Use) (21 CFR 601.70(b)). Submit two copies of the report to the CBER Document Control Center, HFM-99, 1401 Rockville Pike, Rockville, MD 20852-1448. We encourage the electronic submission of 506B reports submitted according to the electronic records requirements described under 21 CFR part 11. You should submit 506B reports separately for each licensed product, but if you are performing multiple 506B studies for the same biological product, all 506B studies should be included in a single postmarketing study commitment annual status report.

Do not include other notifications or submissions in your 506B report. Other notifications, such as manufacturing changes reported under 21 CFR 601.12, should be identified clearly and submitted in a separate report.

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F. Submitting Final Study Reports

When a postmarketing study commitment has been completed or terminated early, you should submit a final report as a separate submission or as a supplement to the NDA, ANDA, or BLA. If you submit a final report as a separate submission, the cover letter should prominently identify the submission as **POSTMARKETING STUDY COMMITMENT — FINAL STUDY REPORT** in bold, capital letters at the top of the letter and should clearly identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter. Similarly, if you submit a final report as a supplement, the top of the cover letter should state **SUPPLEMENT CONTAINS POSTMARKETING STUDY COMMITMENT — FINAL STUDY REPORT** and clearly identify the commitment being addressed. If you do not designate a submission as a final study report, the Agency might not recognize it as such. You should submit the final study report as soon as possible after completing the study.

If a postmarketing study commitment includes multiple studies, the cover letter for the submission of the final completed study should identify the submission dates of reports on all previously concluded and submitted studies. If the final study report is the first report submitted for multiple studies described within a single commitment, the cover letter should indicate that the final study report only partially addresses the commitment.

G. How the FDA Evaluates Fulfillment of and Release from Postmarketing Study Commitments

After a postmarketing study commitment has been completed (i.e., the study has been conducted), you are expected to submit a final study report that describes the study and its results and explain, if necessary, how the study fulfills the requirement or commitment. If the study does not fulfill the requirement or commitment, you should explain why the study was unable to do so and describe your future plans to meet the objective of the commitment.

The Agency will review the final study report and determine whether the commitment has been satisfied. We will notify you, in writing, of our conclusion.

- If we conclude that the study commitment has been met, we will consider the commitment satisfied and will notify you, in writing, that the commitment is considered fulfilled. You will no longer need to report the status of the study commitment in your annual status report.
- If a study was completed but failed to satisfy the purpose of the requirement or commitment, but would still provide useful information and can be addressed through a study of modified design, the Agency may release the original commitment and establish a new postmarketing study commitment and schedule. If the FDA agrees that the failed study is no longer feasible or would not provide useful information, the FDA may release the commitment, and you will no longer need to report the status of the study commitment in your annual status report.

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- If you terminate a study early, you should submit the final study report for that study commitment for FDA review to determine whether the commitment has been satisfied. If you terminate a study that the FDA determines is still feasible, would yield useful information, and can be addressed through a study of modified design, the Agency may release the original commitment and establish a new postmarketing study commitment and schedule. If you terminate a study that the FDA agrees is no longer feasible or would not provide useful information, the FDA may release the commitment, and you will no longer need to report the status of the study commitment in your annual status report. You are encouraged to contact the FDA if you are contemplating the early termination of a postmarketing study commitment.

If you have not undertaken the postmarketing study commitment and we determine the study is no longer feasible or would not provide useful information, we will notify you, in writing, that the commitment is released. You will no longer need to report the status of the study commitment in your annual status report.

IV. CONTENT AND FORMAT OF A POSTMARKETING STUDY COMMITMENT STATUS REPORT

The rule implementing section 506B sets forth the required format and content of the postmarketing study commitment status reports that must be submitted under 21 CFR 314.81(b)(2)(vii) and 601.70(b). These requirements are intended to ensure that the reports you submit contain enough information for the FDA to identify you (the applicant), the product being studied, the specific study being conducted, the status of the study commitment, and the reasons, if any, for your failure to complete the study commitment.

Section 506B requires you to report the status of 506B studies. A postmarketing study commitment ideally consists of one study (i.e., the completion of a single study is expected to fulfill the commitment). In some cases, postmarketing study commitments made before the enactment of section 506B involve conducting multiple studies. When reporting on the progress of multiple studies being conducted under a single postmarketing study commitment, the annual status report should list separately the appropriate information for each study.

You must provide the following information for each postmarketing study commitment submitted under 21 CFR 314.81(b)(2)(vii) or 601.70(b) (see Appendix A for examples).

- **Applicant:** The name of the individual or entity holding the approved NDA, ANDA, or BLA.
- **Product:** The approved product's established or proper name and proprietary name, if any. If the product is distributed under more than one proprietary name, you should include all proprietary names.
- **Application Number:** The NDA, ANDA, or BLA number and supplement number, if any, for which the postmarketing study commitment was made.

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- **NDA, ANDA, or BLA Approval Date:** The date the NDA, ANDA, or BLA was first approved for marketing in the United States. This date will appear on the approval letter for the original application.
- **Date of Postmarketing Study Commitment:** The date of the letter that details the postmarketing study commitment. For study commitments made before or at the time of approval of an original application or supplemental application, the commitment date is the same as the date of the FDA's approval of the original application or supplemental application, as applicable. For commitments made after approval, the commitment date is the date of the FDA's letter confirming the commitment.
- **Commitment Description:** The description must include sufficient information to uniquely describe the study. You should provide the number assigned to each postmarketing study commitment as it appears in the application's approval letter or postmarketing study commitment letter. Your commitment description may include the purpose of the study, the type of study, the patient population addressed by the study, and the indication(s) and dosage(s) that are to be studied (21 CFR 314.81(b)(2)(vii)(a)(6) and 601.70(b)(6)). Generally, the description of the postmarketing study commitment as it appears in the application's approval or postmarketing study commitment letter will provide an adequate description. However, in cases where multiple studies are being conducted, the following information may be needed:
 - Purpose of the study, including study goals, objectives, and endpoints
 - Patient population being studied, including the specific illness or condition, and whether the study targets subpopulations such as pediatric or geriatric subjects
 - Drug dosage or delivery system
 - Specific study protocol number, if applicable
- **Study Schedule:** The original and most recent (if revised) study schedule for conducting, completing, and reporting on the postmarketing study commitment. If more than one study is being conducted under a single commitment, provide a schedule for each study. If the original schedule has been previously revised, provide both the original schedule and the most recently revised schedule in this section of each annual status report (see section III.D.). You should describe the following elements in your schedule:
 - Actual/projected date for submission of study protocol to the FDA
 - Date of completion of patient accrual into the study (or date of first animal dosed)
 - Completion date of the study

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- Submission date of the final study report to the FDA

You may also have an agreement to report important intermediate milestones (e.g., date of initiation of patient accrual, evaluation of surrogate endpoints in a study that also measures clinical benefit). If your study commitment includes a commitment to report at these intermediate milestones, you should include the milestones in the study schedule (21 CFR 314.81(b)(2)(vii)(a)(7) and 601.70(b)(7)). For any milestones that have been met at the time the commitment is made (e.g., submission of the final study protocol), you should report the actual date that the milestone was met in the study schedule.

- **Current Status:** A description of the status of the 506B study. Describe the status of each postmarketing study commitment against the *original* projected study schedule, regardless of whether you have submitted a revised schedule to the FDA. You should describe the status using *only one* of the following terms (21 CFR 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8)):

Pending: The study has not been initiated (i.e., no subjects have been enrolled or animals dosed), but does not meet the criterion for *delayed* (i.e., the *original* projected date for initiation of patient accrual or initiation of animal dosing has not passed).

Ongoing: The study is proceeding according to, or is ahead of, the *original* schedule. The FDA considers a study to be *ongoing* until a final study report is submitted to the FDA, as long as the activities are proceeding according to the *original* study schedule. If patient accrual or animal dosing has started but is not complete, and the projected date for completion of that milestone has passed, the study should be categorized as *delayed*.

Delayed: The progression of the study is behind the *original* study schedule. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final study report to the FDA. While the *original* study schedule — not a revised schedule — serves as the basis for defining a study as *delayed*, each phase of the study will be considered in its own right. If you have one delayed phase, but get back on schedule during the next phase, the *delayed* status will no longer apply.

Terminated: You ended the study before completion, and you have not yet submitted a final study report to the FDA.

Submitted: You have concluded or terminated the study and have submitted a final study report to the FDA, but we have not yet notified you in writing that the study commitment has been fulfilled or that the commitment has been released.

If more than one study is being conducted under a commitment, the status of the overall commitment will be based on the status of the least-progressed study. For example, if

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you are conducting two studies, and both are progressing according to *original* projected schedules, you should categorize the commitment as *ongoing*. If one study is progressing according to the *original* projected schedule but the other is behind schedule, you should categorize the commitment as *delayed*. You can provide information in the “Explanation of Status” section of the report to explain the status of each study under a commitment in an effort to demonstrate progress in that commitment.

- **Explanation of Status:** A brief explanation about how the study is progressing in reference to the original projected study schedule (21 CFR 314.81(b)(2)(vii)(a)(9) and 601.70(b)(9)). This information will be displayed on the Agency Web site for *delayed* and *terminated* studies; therefore, it should be concise and should not include personal privacy information or trade secret information (see example in Appendix A). Provide the following information:
 - A brief description of the status of the study, including the patient accrual or animal dosing rate. Express the patient accrual or animal dosing rate by providing the number of patients/animals you have enrolled/dosed to date and the total number of patients/animals you plan to enroll/dose for the study. To the extent necessary, the particular status described under 21 CFR 314.81(b)(2)(vii)(a)(8) or 601.70(b)(8) should be explained.
 - If you are unable to meet the *original* study schedule or any revised schedule (submitted under the study schedule section), provide a revised schedule and the reasons for the revision.

V. TIME FRAMES FOR THE FDA’S REVIEW OF ANNUAL STATUS REPORTS AND FINAL STUDY REPORTS

The FDA intends to review postmarketing study commitment annual status reports and final study reports according to the following time frames.

A. Annual Status Reports

Generally, the FDA will review annual status reports within 3 months of receipt. If we do not agree with your categorization of the status of the study and/or your explanation of status, we will contact you for clarification. We will change the reported study categorization if we find that the status category is not supported.

B. Final Study Reports

Final study reports are often submitted as a supplemental application to modify product labeling. When this occurs, the FDA will review the submission under established review times for supplements (e.g., for Prescription Drug User Fee Act (PDUFA) products). In some cases, a postmarketing study commitment will not yield information that affects product labeling, and the

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final study report will be submitted without a supplemental filing. In such cases, we will generally review the final study report within 1 year of receipt.

VI. INFORMATION ABOUT POSTMARKETING STUDY COMMITMENTS THAT WILL BE AVAILABLE TO THE PUBLIC

Section 506B of the Act states that “[a]ny information pertaining to a [postmarketing status] report shall be considered to be public information to the extent that the information is necessary (1) to identify the sponsor; and (2) to establish the status of [the] study and the reasons, if any, for any failure to carry out the study” (21 U.S.C. 356b(b)). This provision is applicable to all 506B reports. Section 506B provides the FDA with statutory authority to disclose information, including certain information that may be considered to constitute confidential commercial information. However, the FDA will not make public any trade secrets,³ or any information that, if disclosed, might cause an unwarranted invasion of personal privacy.⁴

The FDA will publish an annual *Federal Register* report on the status of postmarketing study commitments and will maintain information about postmarketing study commitments on an Agency Web site. The information in the *Federal Register* report and on the Web site will be based on the verification of information submitted in your annual status reports and information from the Agency’s outgoing approval and postmarketing study commitment letters. Although you may wish to submit interim information about a study (e.g., the date patient accrual was actually completed), such interim information will not be used to change the status of a study commitment. We will update the status of a study commitment when we complete our review of the final study report and issue our determination regarding whether the commitment has been fulfilled or you have been released from the commitment, or after verification of the information submitted in your annual status report.

***Federal Register* report.** As previously discussed, section 506B(c) also requires that the FDA publish annually in the *Federal Register* a report on the status of postmarketing studies that are required or that you have agreed to conduct and for which you have submitted status reports. The information that the FDA publishes in the *Federal Register* report will include the following:

- The number of applicants with open postmarketing study commitments
- The number of open postmarketing study commitments

³ “A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.” (21 CFR 20.61(a))

⁴ See, for example, 21 CFR 20.63(a), “The names or other information which would identify patients or research subjects in any medical or similar report, test, study, or other research project shall be deleted before the record is made available for public disclosure.”

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- The number of applications with open study commitments for which annual reports were due but not submitted by the sponsor within 60 days of the anniversary date of the product's U.S. approval
- The number of concluded postmarketing study commitments:
 - That fulfilled the terms of the commitment
 - For which a study was completed but failed to satisfy an applicant's commitment
 - For which a study was not done and the FDA deemed it was no longer feasible or would no longer provide useful information and released the commitment

Agency Web site (<http://www.fda.gov/cder/pmc>). To provide public access to certain information on the status of specific postmarketing studies, the FDA displays detailed information on an Agency Web site. The information included on the Web site (see Appendix B) comes from our review of annual 506B reports and the Agency's outgoing approval and postmarketing study commitment letters. This information allows the public to follow the progress of 506B studies of specific interest. The Web site includes the following information:

Applicant:

Product:

NDA/BLA/ANDA Number:

Supplement Number:

NDA/BLA Approval Date:

Annual Report Due Date:

Annual Report Received Date:

Commitment Number:

Commitment Required Under: [*if the commitment is a required study*]

Original Projected Completion Date: [*if available*]

Commitment Description:

Current Status:

Explanation of Status: [*for delayed and terminated studies only*]

In establishing the FDA Web site, both CDER and CBER use data from their electronic databases to identify postmarketing study commitments for which an annual status report was expected, but not submitted.

The FDA posts study schedule information on the Web site to the extent necessary to explain the status of a study. If a commitment did not have a schedule, and the Agency did not receive an annual postmarketing study commitment status report, the commitment is categorized according to the most recent information available to the Agency.

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There may be instances when you disagree with the FDA's categorization of the status of a study as it appears on the Web site. If this happens, you may contact us by e-mail at pmcweb@cder.fda.gov so that we can explain the displayed status or update it accordingly.

The FDA Web site will continue to list postmarketing study commitments for no more than 1 year from the date of the FDA's letter confirming that the commitment was fulfilled or released. After that time has passed, all references to the study will be removed from the Web site. The information on the FDA Web site is updated quarterly in January, April, July, and October.

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GLOSSARY

In reporting the status of postmarketing study commitments, you should know and understand the following terms:

506B Report: A status report, submitted annually by applicants within 60 days of the anniversary of the FDA's approval of the product, reporting on the progress of 506B studies (21 CFR 314.81(b)(2)(vii) and 601.70). A 506B report is required until the FDA notifies the applicant, in writing, that the Agency concurs that the study commitment has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

506B Study: A study conducted after approval that the FDA has required you to conduct or that you have agreed, in writing, to conduct, and that concerns a product's clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology.

Final Study Report: A final report providing information to complete part or all of a postmarketing study commitment. When a commitment includes multiple studies, a single final study report may or may not complete all parts of the commitment.

Postmarketing Study: A trial or other investigation, conducted after marketing approval under a single protocol, to gather specific information about an approved drug or biological product.

Postmarketing Study Commitment: An agreement between you and the FDA, confirmed in writing, for you to conduct one or more 506B or CMC studies. Also includes 506B studies that are *required* by the FDA (e.g., accelerated approval clinical benefit studies, animal efficacy clinical benefit and safety studies, deferred pediatric studies under PREA).

Projected Final Study Report Submission Date: The projected date by which the final study report will be submitted to the FDA. When a commitment includes multiple studies, the projected final study report submission date is the date by which the final study report will be submitted to address the last outstanding study in the commitment.

Projected Protocol Submission Date: The projected submission date by which the final protocol for the postmarketing study will be submitted.

Projected Study Initiation Date: The projected date by which patients will begin enrollment in a clinical study, or the date the first animal will be dosed in a nonclinical toxicology study.

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**APPENDIX A:
SAMPLE X POSTMARKETING STUDY COMMITMENTS
ANNUAL STATUS REPORT**

(Submitted by the Applicant)

Note: Certain information from this report will be displayed on the FDA Web site, <http://www.fda.gov/cder/pmc>.

Postmarketing Study Commitments Annual Status Report: Submitted 02/01/2000.

Applicant: AABBCC Pharmaceuticals, Inc.

Product: Efficacymycin (Curritt)/Oral, chewable tablets (25 mg; 50 mg)

NDA/BLA/ANDA Number: 12-345

NDA/BLA/ANDA Approval Date: 12/31/97

Commitment Date: 12/31/97

Commitment Number: 1

Description of Study Commitment: Evaluate the safety and efficacy of Curritt in pediatric patients. Study is an open-label, randomized comparison to amoxicillin in cohort ages 2-4 and 6-12 years. Study will include approximately 400 patients with confirmed urinary tract infection. Dosage: 25 mg oral chewable tablets.

Original Schedule for Conduct and Reporting of Study: Final protocol will be submitted to the FDA for review by 02/01/98. Study enrollment will begin by 06/01/98, with enrollment concluded by 12/01/99. Last patients should complete evaluations by 04/01/00. Study final report will be submitted to the FDA by 10/01/00.

Current Status: Ongoing

Explanation of Status: Study completed enrollment of 408 patients on schedule and all patient evaluations were concluded 01/15/00. Study is closed. Clinical monitors are in the process of verifying data. Study final report should be submitted on schedule.

Supplement Number: 005

Commitment Date: 02/23/99 (NDA supplement 12-345/S-005: 50 mg oral chewable tablets)

Commitment Number: 1

Description of Study Commitment: Evaluation of 50 mg Curritt in patients with impaired liver function. Study to include approximately 100 patients (30 with normal liver and renal function).

Original Schedule for Conduct and Reporting of Study: Protocol was approved at time of study commitment (02/23/99). Study enrollment to begin 08/01/99 with enrollment to be concluded by 05/01/00. Last patients should complete evaluations by 10/01/00. Study final report will be submitted to the FDA by 02/01/01.

Revised Schedule for Conduct and Reporting of Study: [Revised 02/01/2000]. A revised protocol will be submitted to the FDA by 06/01/00. Study enrollment will conclude by 12/03/00. Current study completion date is now anticipated by 06/01/01 with a study final report to the FDA by 11/24/01.

Current Status: Delayed

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Explanation of Status: No patients have been enrolled. Two IRBs have raised issues that must be addressed by revising the study protocol.

Commitment Number: 2

Commitment Date: 02/23/99 (NDA supplement 12-345/S-005: 50 mg oral chewable tablets)

Description of Study Commitment: Evaluation of 50 mg Curritt in patients with impaired renal function. Study to include approximately 60 patients (15 normal).

Original Schedule for Conduct and Reporting of Study: Protocol was approved at time of study commitment (02/23/99). Study enrollment started 08/01/99 with enrollment to be concluded by 05/01/00. Last patients should complete evaluations by 10/01/00. Study final report will be submitted to the FDA by 02/01/01.

Current Status: Ongoing

Explanation of Status: A total of 57 patients completed the study. Study report in preparation. The study final report will be submitted to the FDA by 02/01/01.

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**APPENDIX B:
SAMPLE X POSTMARKETING STUDY COMMITMENT
STATUS SUMMARY**

[To be displayed on the FDA Web site]

Applicant: AABBCC Pharmaceuticals, Inc.

Product: Efficacymycin (Curritt)/Oral, chewable tablets (25 mg; 50 mg)

NDA/BLA/ANDA Number: 12-345

NDA/BLA Approval Date: 12/31/97

Annual Report Due Date: 12/31/99

Annual Report Received: 02/01/00

Commitment Number: 1

Original Projected Completion Date: 10/01/00

Commitment Description: Evaluate the safety and efficacy of Curritt in pediatric patients. Study is an open-label, randomized comparison to amoxicillin in cohort ages 2-4 and 6-12 years. Study will include approximately 400 patients with confirmed urinary tract infection. Dosage: 25 mg oral gelatin capsules.

Current Status: Ongoing

Applicant: AABBCC Pharmaceuticals, Inc.

Product: Efficacymycin (Curritt)/Oral, chewable tablets (25 mg; 50 mg)

NDA/BLA/ANDA Number: 12-345

Supplement Number: 005

NDA/BLA Approval Date: 12/31/97

Annual Report Due Date: 12/31/99

Annual Report Received: 02/01/00

Commitment Number: 1

Original Projected Completion Date: 02/01/01

Commitment Description: Evaluation of 50 mg Curritt in patients with impaired liver function. Study to include approximately 100 patients (30 with normal liver and renal function).

Current Status: Delayed

Explanation of Status: No patients have been enrolled. Two IRBs have raised issues that must be addressed by revising the study protocol.

Commitment Number: 2

Original Projected Completion Date: 02/01/01

Description of Study Commitment: Evaluation of 50 mg Curritt in patients with impaired renal function. Study to include approximately 60 patients (15 normal).

Current Status: Ongoing

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[Note: Postmarketing study commitment information is displayed on the Web site as one application per page. Thus, in this example, the information for Commitment Number 1 established under the original application would display on a separate Web page from the postmarketing study commitment information for Commitment Numbers 1 and 2 established under supplement application number 005, as shown above.]