Guidance for Industry

Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997

DRAFT GUIDANCE

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For questions on the content of the draft document, contact (CDER) James L. Cobbs, 301-594-5610, or (CBER) Sharon T. Risso, 301-827-5098.

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 2001

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Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997

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Guidance for Industry[1]

Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997

This guidance represents the Agency's current thinking on the submission of postmarketing study reports for human drug and licensed biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the regulated industry. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

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 Postmarketing Studies) to the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 356b). Section 506B provides FDA with additional authority for monitoring the progress of postmarketing studies that drug and biologics applicants have agreed to conduct.

Under section 506B(a), applicants who are required by FDA, or who have entered into an agreement with FDA, to conduct a postmarketing study are now required to provide the Agency with an annual report on the status of the study until it is completed or terminated. These annual reports must address the progress of the study or the reasons for the failure of the applicant to conduct the study (21 U.S.C. 356b(a)).

Section 506B also requires FDA to keep the public and medical community informed about the postmarketing obligations and activities of applicants. More specifically, under section 506B(c), FDA must develop and publish annually in the *Federal Register* a report on the status of postmarketing studies that applicants have agreed to conduct and for which status reports have been submitted (21 U.S.C. 356b(c)). For these purposes, section 506B(b) indicates that any information necessary to identify the sponsor of a study and establish the status of a study and the reasons, if any, for any failure to carry out the study, shall be considered to be public information (21 U.S.C. 356b(b)).

Finally, section 130(b) of the Modernization Act directs FDA to submit a special postmarketing study report to Congress by October 1, 2001. In this report, FDA must: (1) Summarize the status reports that have been submitted under section 506B; (2) evaluate the performance of applicants in

[1] This guidance has been prepared by FDA's Postmarketing Studies Working Group which includes representatives from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

fulfilling their postmarketing study commitments; (3) evaluate the Agency's timeliness in reviewing the postmarketing studies it has received; and (4) make any necessary legislative recommendations concerning postmarketing studies.

On December 1, 1999, the agency published in the *Federal Register* a proposed rule (62 FR 67207) to implement section 506B. On October 30, 2000, the agency published the final rule (65 FR 64607), and by *Federal Register* notice published on February 20, 2001 (66 FR 10815), FDA delayed the effective date of the rule until April 30, 2001. The final rule makes several changes to the existing regulations for approved human drugs and licensed biological products. This guidance complements the rule by describing in greater detail the content, format, and timing of the postmarketing study reports required by section 506B. This guidance also describes (1) FDA's timeframes for reviewing the status reports it receives; (2) how FDA will make information about postmarketing studies public; and (3) what that information will be.

II. BACKGROUND

A. Reasons for Conducting and Types of Postmarketing Studies

Postmarketing studies are those performed by you, a drug or biologics applicant, after FDA has granted approval to market its product. Such studies are used to gather additional information about product safety, efficacy, or optimal use. Postmarketing studies are also used to evaluate chemistry, manufacturing, and control (CMC) issues, which are important for ensuring consistency and reliability in drug production.

Generally, you would undertake a postmarketing study under one of the following three circumstances:

1. FDA might require you to conduct a postmarketing study as a condition of marketing approval. Accelerated approval clinical benefit studies and deferred pediatric studies are two examples of this.

    a. Accelerated Approval Clinical Benefit Studies. When FDA approves a drug in accordance with the accelerated approval provisions (21 U.S.C. § 356, 21 CFR 314.510 and 601.41), the agency usually requires you to conduct postmarketing studies to verify and describe the drug's clinical benefits. If the studies do not demonstrate effectiveness, if they reveal safety problems, or if they are not completed with due diligence, FDA can withdraw approval of the drug (21 U.S.C. § 356(b)(3), 21 CFR 314.530 and 601.43).

    b. Deferred Pediatric Studies. For certain drugs that are used in, or have the potential to be used in, pediatric populations, you are required to assess the safety and effectiveness of those drugs in all relevant pediatric subpopulations (21 CFR 314.55 and 601.27).

FDA may permit these studies to be deferred and performed as postmarketing studies.

2. A postmarketing study might be conducted because you and FDA agree it should be performed. Such agreements can be reached either before or after FDA has granted marketing approval to your drug. If you and FDA agree before approval of the drug that a postmarketing study should be performed, the study will likely be used to address some concern about the safety, benefit, or use of the drug that does not warrant delaying approval of the application. If you and 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.

3. A postmarketing study might be conducted on your own initiative without any request or requirement by FDA. Applicants conduct postmarketing studies on their own initiative for a variety of reasons, including the evaluation of a new indication or a new delivery system for a drug.

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

1. Scope

To implement section 506B of the act, in the *Federal Register* of October 30, 2000 (65 FR 64607), FDA made several changes to the existing postmarketing reporting regulations for both human drug products and licensed biological products. These changes are summarized below.

First, the rule distinguishes different types and purposes of postmarketing studies. FDA has focused its authority under section 506B on postmarketing studies that concern a drug's clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology, because these are the studies that relate most directly to a drug's safety or its effect on the disease or condition being treated. If a postmarketing study fits one of these four categories, we will include information about its status in the agency's annual *Federal Register* report on postmarketing studies and in the agency's special report to Congress. Such studies might include evaluating a drug's effect on:

- survival or long-term morbidity;
- effectiveness in a different disease, or in a different phase of the same disease; or in a different population (e.g., children or elderly); or
- how pharmacokinetics are altered in special populations, such as the elderly or renally impaired; or
- how interactions with other drugs or foods affect safety or effectiveness; or
- humans or animals to determine if long-term administration causes serious adverse events.

You will still report other types of postmarketing studies (e.g.; product stability studies, product dissolution studies, or the development of an improved potency assay) to FDA, but information about them will not be made public in the annual *Federal Register* reports or special report to Congress.

Second, the rule applies only to postmarketing studies that FDA has required or that you have agreed with FDA, in writing, to conduct. In this guidance, we refer to studies that are required to be conducted and studies you have agreed to conduct as postmarketing study commitments. Section 506B does not apply to studies that you conduct without a commitment to, or a requirement by, FDA.

Third, the rule applies only to approved human drug products and licensed biological products that meet the definition of *drug* under the act. It does not apply to biological products that meet the definition of *medical 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. 360l. It also does not apply to veterinary drug products, which will be addressed separately by the Center for Veterinary Medicine.

Fourth, the rule applies only to approved applications. It does not apply to applications that have been withdrawn after approval.

2. Specific Provisions

a. Human Drug Products

Under FDA's previous postmarketing reporting regulations for human drug products, you, as a holder of a new drug application (NDA) or abbreviated new drug application (ANDA), were required to submit to FDA an annual report that contained a statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant (21 CFR 314.81(b)(2)(vii)). The rule amends 21 CFR 314.81(b)(2)(vii) and creates new sections 314.81(b)(2)(viii) and (b)(2)(ix).

- Under amended 21 CFR 314.81(b)(2)(vii), you must provide FDA with status reports on each postmarketing study being performed by you or on your behalf concerning clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology if we required the study or if you agreed with FDA, in writing, to conduct the study.

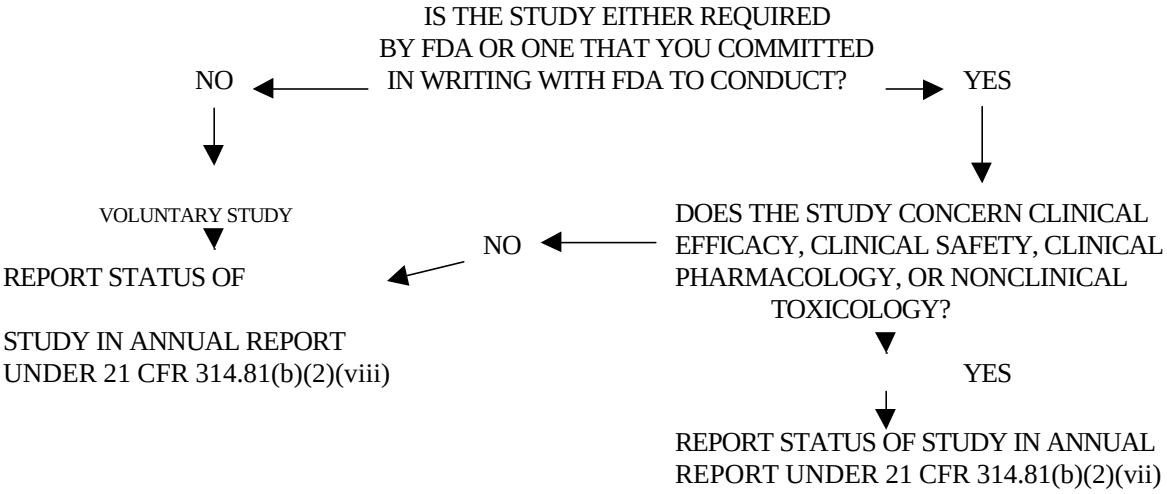
- The contents of status reports submitted under 21 CFR 314.81(b)(2)(vii) with the exception of any schedule for completion submitted under 21 CFR 314.81(b)(2)(vii)(a)(7) will be included in FDA's annual report published in the *Federal Register* and in FDA's

special report to Congress. In addition, FDA will post this information on FDA's website.

- Under new 21 CFR 314.81(b)(2)(viii), you must provide FDA with status reports on all other postmarketing studies being performed by you or on your behalf. The rule clarifies that you are required to include results from any CMC studies, which you have agreed to conduct, and from all ongoing stability studies.

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

NDA/ANDA REPORTING REQUIREMENTS FOR POSTMARKETING STATUS STUDIES



b. Licensed Biological Products

- Under existing rules, you, as an applicant for a biological product marketed under a biologics license application (BLA), are required under 21 CFR 601.12(d) to submit an annual report for certain changes made to your approved application, but you are not generally required to submit annual reports on the status of postmarketing studies. Postmarketing pediatric studies required under 21 CFR 601.28 are the one exception to this rule. To implement section 506B of the Act, the new final rule amends the biologics regulations by adding a new postmarketing annual reporting requirement, 21 CFR 601.70, and by revising the pediatric reporting requirement at 21 CFR 601.28.

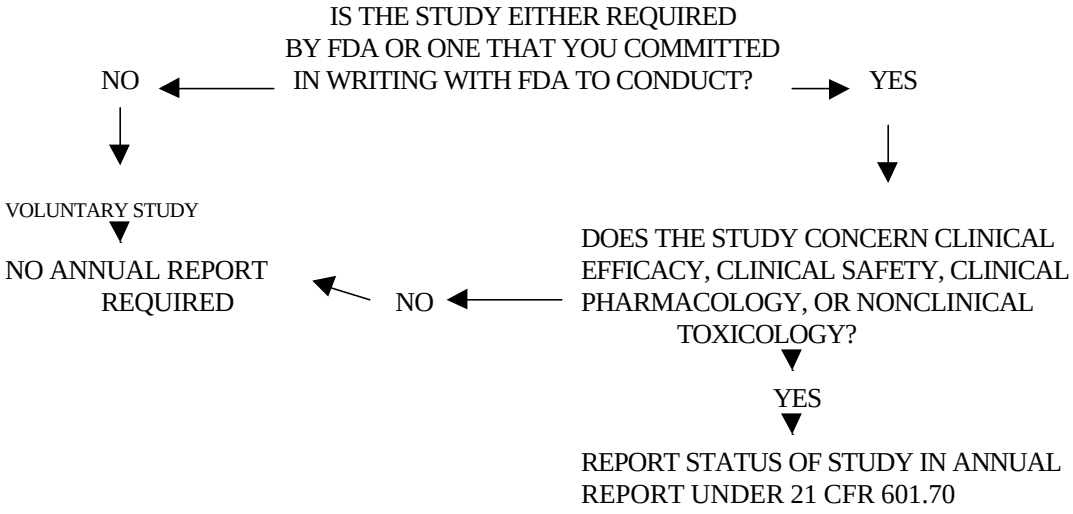
- Under new 21 CFR 601.70, you must provide FDA with status reports on each postmarketing study being performed by you or on your behalf concerning clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology if we required the study or if you agreed with FDA, in writing, to conduct the study.

- Status reports on all other postmarketing studies (e.g., chemistry, manufacturing, and control studies), including postmarketing studies that you conduct without commitment to, or requirement by, FDA, do not need to be reported under 21 CFR 601.70. However, if you choose to provide FDA with a status report on such a study, you can do so under 21 CFR 601.70.

- Section 601.28 has been amended to require that the status of postmarketing pediatric studies that fall within the scope of 21 CFR 601.70 be reported to FDA under 21 CFR 601.70 rather than under 21 CFR 601.28.

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

BLA REPORTING REQUIREMENTS FOR
POSTMARKETING STATUS STUDIES



III. PROCEDURES CONCERNING POSTMARKETING STUDY STATUS REPORTS

A. Definitions of Terms Used in Reporting Postmarketing Studies

In reporting the status of postmarketing studies, you should know and understand the following terms.

A **postmarketing study** is a clinical trial or other investigation, usually conducted under a single protocol, to gather specific information about an approved drug or biological product.

A **postmarketing study requirement** is a requirement by FDA that you conduct a study, e.g.; accelerated approval clinical benefit studies.

A **postmarketing study commitment** is an agreement by you, and confirmed by FDA in writing, to conduct one or more studies or to provide other additional information concerning your approved drug or biological product.

Section 506B requires you to report the status of postmarketing studies that are required to be conducted (postmarketing study requirements) and studies you have agreed to conduct (postmarketing study commitments). We refer to both postmarketing requirements and commitments as "commitments" in this document. A postmarketing commitment will usually consist of one study, i.e.; the completion of a single study will fulfill the postmarketing study commitment. In some cases, especially for drugs and biological products with commitments made prior to enactment of 506B, a postmarketing commitment may involve conducting multiple studies. If multiple studies are being conducted under a single postmarketing commitment, the annual status report should identify each study in the Description of the Postmarketing Commitment subsection of the status report and categorize the status of each individual study in the Current Status subsection of the report. (See Section IV. Content and Format of a Postmarketing Study Commitment Status Report.)

B. Postmarketing Study Protocols: When and How to Submit Them

The type of study and the agreements you reached with the agency before product approval will influence when the final protocol for a postmarketing study should be submitted. Generally, protocols for required studies (e.g., accelerated approval clinical benefit studies) should be submitted prior to application approval, and protocols for other postmarketing studies should be submitted within three months after the date of the postmarketing study commitment.

Protocols for 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 BLA. Protocols for studies not requiring an IND (e.g., toxicology studies) should be

submitted to the NDA, ANDA, or BLA. All submissions should be clearly labeled **Postmarketing Study Protocol**.

In all cases, the submission of the final protocol for studies required or agreed to, should be accompanied by a proposed schedule outlining times for completion of patient enrollment (or initiation of an animal study, if applicable), completion of the study, and submission of the final report to FDA. In addition, there may be additional study milestones for which it is agreed that information or data will be submitted to FDA. An example is the submission of data on surrogate endpoints in a study also measuring clinical benefit. If additional milestones for reporting information are part of a study commitment, such milestones should be included in the proposed schedule submitted to FDA. We will use the schedule submitted in the first postmarketing study status report under 21 CFR 314.81(b)(2) or 601.70 as the original schedule for studies that are already ongoing and for which a schedule was not proposed at the time of the postmarketing study commitment. You do not need to provide schedules for studies conducted without commitment to, or requirement by, FDA.

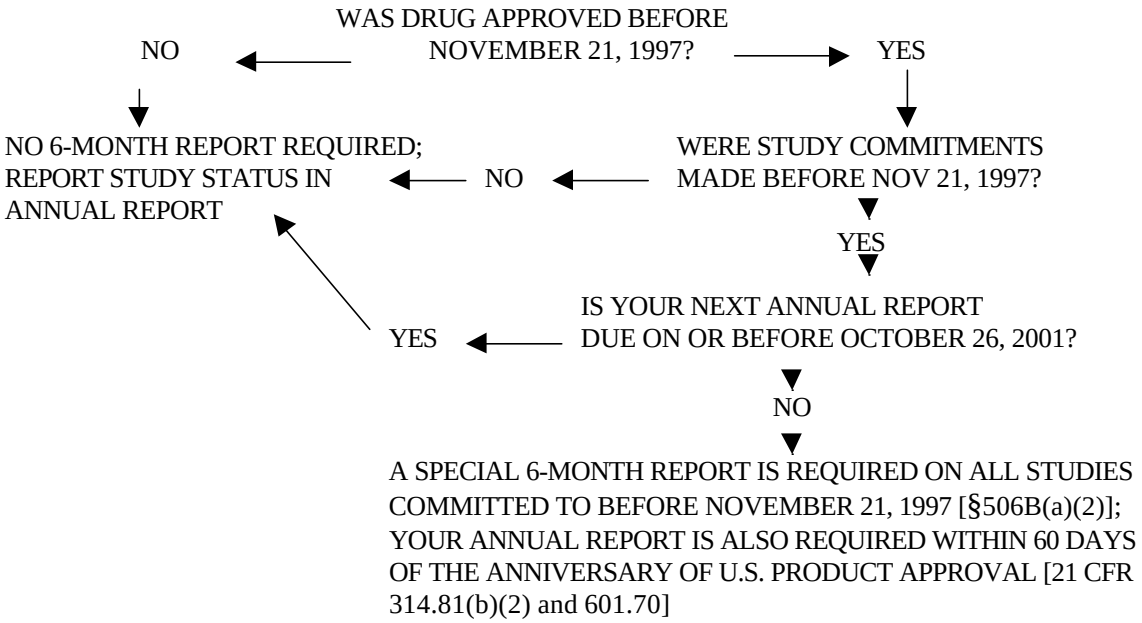
C. When Should You Submit Your Postmarketing Study Status Reports?

Postmarketing study status reports for both human drugs and biological products should be submitted annually until a final study report has been submitted to FDA and we have notified you that the study commitment has been met (see below, section III.D). The annual status reports required by 21 CFR 314.81(b)(2) and 601.70 are due within 60 days of the anniversary of the NDA, ANDA, or BLA approval in the United States.

Section 506B of the act contains a special provision, however, for postmarketing study agreements that were made before the date the Modernization Act was enacted (November 21, 1997). Under section 506B(a)(2), the initial report for all postmarketing study commitments entered into before the Modernization Act was enacted must be submitted within 6 months after the date that FDA regulations implementing section 506B become effective (April 30, 2001), even if that six month period does not include the regular annual report due date. For purposes of implementing this statutory requirement, FDA will regard study commitments made before or at the time of approval of an application or supplement to have been made on the same day the application or supplement was approved.

The following chart is a quick reference for determining if you need to submit a special 6-month report.

DO I NEED TO SUBMIT A 6-MONTH STATUS REPORT?



Applicants who are required to submit a 6-month status report, and whose anniversary date of U.S. product approval falls between October 27 and December 26, 2001, may choose to file their annual status reports early, on October 26, 2001, or an earlier date within 60 days of the anniversary of U.S. product approval [21 CFR 314.81(b)(2) and 601.70]. Applicants who fall within this category, and choose to file their annual reports early, would satisfy in a single filing their obligations to submit a 6 month status report on or before October 26, 2001, and to submit an annual report of postmarketing studies within 60 days of the anniversary of U.S. product approval.

IF I AM REQUIRED TO SUBMIT A 6 MONTH REPORT, CAN I SATISFY MY 6 MONTH STATUS REPORT REQUIREMENT BY FILING MY ANNUAL POSTMARKETING STUDY STATUS REPORT EARLY?

Is the anniversary date of the approval between 10/27/01 and 12/26/01?

No.	Yes.
You must file both a 6 month and an annual postmarketing study status report	You may choose to file your annual report up to 60 days early, as long as that date is on or before 10/26/01. This single filing would satisfy both the 6-month and the annual requirements.

D. How Should Applicants Submit Their Postmarketing Study Status Reports?

1. Human Drug Products

For human drug products, postmarketing status reports that are submitted in an annual report under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) should be clearly segregated in different report sections and should be accompanied by Form FDA-2252 (Transmittal of Annual Reports for Drugs for Human Use). The cover letter should clearly identify the submission as a **6-Month Report on Postmarketing Studies** or as an **Annual Report on Postmarketing Studies**, as applicable. For 6-month reports, "Other" should be checked in Box 6 of the form FDA 2252. If you were required to submit a 6-month report, you should include updated status information for those studies under 21 CFR 314.81(b)(2)(vii) in your complete annual report, which is due within 60 days of the anniversary of the NDA or ANDA approval.

Annual reports and 6-month reports for human drug products regulated by CDER should be sent to the CDER division responsible for reviewing the application. Annual reports and 6-month reports for human drug products regulated by CBER should be sent to the CBER Document Control Center, HFM-99.

2. Licensed Biological Products

For licensed biological products, postmarketing status reports that are submitted in an annual report under 21 CFR 601.70 should be limited to a single licensed product and be accompanied by a Form FDA-2252 (Transmittal of Annual Reports for Drugs for Human Use). The cover letter should clearly identify the submission as a **6-Month Report on Postmarketing Studies** or as an **Annual Report on Postmarketing Studies**, as applicable. Two copies of the report should be submitted to the CBER Document Control Center, HFM-99. If you are performing multiple postmarketing studies for the same biological product, the status for all the

studies should be included in a single postmarketing annual report. If you were required to submit a 6-month report, you should include updated status information for those studies under 21 CFR 601.70 in your complete annual report, which is due within 60 days of the anniversary of the BLA approval.

If you are performing postmarketing studies other than those for which an annual report is required (e.g., product stability or process validation studies), you may submit status updates for those studies in the report under 21 CFR 601.70, but the reports on those studies should be clearly segregated in a separate report section. Do not include other notifications or submissions in this report. Other notifications, such as those made under 21 CFR 601.12 should be identified clearly and submitted in a separate report.

E. How Should Study Final Reports be Submitted?

When a postmarketing study has been completed, you should submit a final report as a separate submission to the NDA, ANDA, or BLA in an original and 2 copies with form FDA 356h and a cover letter attached. The cover letter, regardless of the type of submission (e.g., supplement, annual report, other), should always prominently identify the submission as **POSTMARKETING COMMITMENT – STUDY FINAL REPORT** in bolded block letters at the top of the letter and should clearly identify the commitment being addressed (i.e., refer to the commitment wording and number, if any, used in the approval letter). If you do not designate a submission as a study final report, the agency will not be able to recognize it as such and may not review the submission under the procedures described in this guidance.

If a postmarketing commitment includes multiple studies, the study final report is the report that addresses the last outstanding study of that commitment. The cover letter should identify the submission dates of all previously submitted concluded study reports.

F. How will FDA Evaluate Postmarketing Study Final Reports?

The study final report should describe the study and its results and explain, if necessary, how the study fulfills the requirement or commitment. If the report does not describe a study fulfilling the requirement or commitment, you should explain why the study was unable to do so. The agency will review the final report and determine whether or not the commitment has been satisfied. FDA will notify you, in writing, of our conclusion. If we conclude that (1) the study commitment has been met, or (2) the study is either no longer feasible or would no longer provide useful information, the status of the study will no longer need to be reported in your annual report and the commitment will be considered satisfied. If we conclude that the study is no longer feasible, but that the postmarketing study commitment remains important and can be addressed through a study of modified design, the original study may be terminated with no further reporting and a new postmarketing study commitment and schedule established.

If the study was completed, but failed to meet the requirement or commitment objectives, or if you terminate a study and FDA determines that the study is feasible and would yield useful information, the agency may ask you to undertake another study to fulfill the commitment. Your progress in conducting another study will then be reported in your annual report. You are encouraged to communicate with FDA if you are contemplating early termination of a postmarketing study.

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. These requirements are intended to ensure that the reports you submit contain enough information for FDA to identify you (the applicant), the product being studied, the specific study being conducted, the status of the study, and the reasons, if any, for your failure to complete the study.

You should provide the information listed below for each postmarketing study commitment submitted under 21 CFR 314.81(b)(2)(vii) or 601.70. Appendix A to this guidance document provides examples of how these reports should be formatted. When more than one study is being conducted to respond to a single commitment, you should list appropriate information for each study separately.

- **Applicant Name**. The name of the individual or entity holding the approved BLA, NDA or ANDA.

- **Product name**. The approved product s established name and proprietary name. If the product is distributed under more than one proprietary name, all proprietary names should be included. The report should also include product dosage form, strength, and route of administration.

- **Application number**. The NDA number, ANDA number, or BLA number and supplement number, if any, for which the postmarketing commitment was made.

- **Date of NDA, ANDA, or BLA approval in the United States**. 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**. For study commitments made before or at the time of approval of an original application or supplemental application, this date is the same as the date of FDA's approval of the original application or supplemental application, as applicable. For commitments made after approval, this is the date of FDA's letter confirming the commitment.

- **Description of the postmarketing commitment**. You should include sufficient information to clearly identify each study being conducted, especially when more than one study is being conducted to meet a particular commitment. To ensure correct identification of the commitment, you should use wording and numbering, if any, as it appears in the original approval or commitment letter. In most cases, this language will be sufficient to identify the commitment. However, in cases where multiple studies are being conducted to address a commitment, additional information may be needed. Such information may include:

    1. Purpose of the study, including study goals and objectives;
    2. patient population being studied, including the specific illness or condition and whether the study targets subpopulations such as pediatric or geriatric subjects;
    3. the drug dosage or delivery system; or
    4. a specific study protocol number, if applicable.

- **Original Schedule for conducting, completing, and reporting the postmarketing study commitment**. If more than one study is being conducted under a single commitment, you should provide a schedule for each study, if the schedule for each is different. The schedule submitted in this section of the report should be the original schedule established by the applicant and FDA. We recognize that study phases may vary depending on the type and design of the study being conducted. However, in conducting a study certain milestones are common and important to determining study progress. These include:

    1. the submission of the study protocol to FDA;
    2. completion of patient accrual into the study (or initiation of an animal study);
    3. completion of the study; and
    4. submission of the final study report to FDA.

    You should provide the projected dates for these phases of the study in the original schedule you submit to FDA. In addition, you may have an agreement to report important intermediate milestones (e.g.; evaluation of surrogate endpoints in a study that also measures clinical benefit). If your study commitment includes reporting at such intermediate milestones, these milestones should be included in the projected schedule. For any milestones that have been met at the time the commitment is made (e.g., submission of study protocol), the actual date should be used. Although situations may arise that will require revision of the original schedule (see explanation of the status of the study), we will use the original schedule for determining the study progress and status. Therefore, you should continue to report the original schedule in this section.

- **Current status of the postmarketing study commitment**. You should describe the status of each postmarketing study against the original schedule using one of the following terms:

    1. **Pending**. The study has not begun (i.e., no subjects have been enrolled), but the projected date for patient accrual has not passed. If the study has not been initiated by the projected date for completion of patient accrual, the study should be categorized as delayed.

    2. **Ongoing**. The study is proceeding according to, or is ahead of, the original schedule described above. A study will be considered to be ongoing until a final study report is submitted to the agency, as long as the activities are proceeding according to the original schedule.

    3. **Delayed**. The study is proceeding but is behind the original schedule described above. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final report to FDA. The original schedule serves as the basis for defining a study as delayed, even if a revised schedule has been provided.

    4. **Terminated**. The study was ended before completion, you do not intend to complete the study as it was originally designed, and you have not yet submitted a final study report to FDA.

    5. **Submitted**. The study has been concluded or terminated and you have submitted a final study report to FDA, but we have not yet advised you that the study commitment has been met.

    If more than one study is being conducted under a commitment, the status of the overall commitment will be based on the progress of all studies. For example, if there are two studies and both are progressing according to projected schedules, you should categorize the commitment as ongoing. If one study is progressing according to the projected schedule but the other is behind schedule, the commitment should be categorized as delayed.

- **Explanation of the status of the study**. To assist FDA in evaluating the progress of postmarketing studies and in processing study status reports more expeditiously, you should include a brief explanation about how the study is progressing in reference to the original schedule. This section of the report should include:

    1. A brief description of the status of the study, including the patient accrual rate. The patient accrual rate should be expressed by providing the number of patients you have enrolled to date and the total planned enrollment for the study. To the extent necessary, the particular status category chosen should be explained.

2. A revised schedule, if the study schedule has changed since the last annual report. If you are unable to meet the original schedule (or the most recent revised schedule) you should provide a revised timeline for study completion and an explanation of the basis for the revision.

V. TIMEFRAMES FOR FDA'S REVIEW OF POSTMARKETING ANNUAL STATUS REPORTS AND STUDY FINAL REPORTS

FDA will review annual postmarketing status reports and postmarketing study final reports according to the following timeframes:

A. Annual Status Reports

Generally, FDA will review annual status reports within three months of receipt. If FDA does not agree with your categorization of the status of the study, we will contact you for clarification and will change the reported study categorization if we find that the status category is not supported by adequate information.

B. Study Final Reports

Many study final reports will be submitted with a supplemental application to modify product labeling. When this occurs, FDA will review the submission under established review times for supplements (e.g., for Prescription Drug User Fee Act (PDUFA) products see letters from the Secretary of Health and Human Services to the Chairman of the Committee on Commerce of the House of Representatives and the Chairman of the Committee on Labor and Human Resources of the Senate, as set forth in the Congressional Record). In some cases, a postmarketing study will not yield information that affects product labeling, and the study final report will be submitted without a supplemental filing. In such cases, we will generally review the study final report within 1 year of receipt.

VI. INFORMATION ABOUT POSTMARKETING STUDIES 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 applicant; 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)). FDA is applying this provision to all postmarketing status reports required by 21 CFR 314.81(b)(2)(vii) and 601.70. Section 506B provides FDA with statutory authority to disclose data and information, including certain information that may be considered to constitute confidential commercial information. However,

FDA will not make public any trade secrets,[2] or any information the disclosure of which might cause an unwarranted invasion of personal privacy.[3]

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

- The number of applicants with outstanding postmarketing study commitments;
- The number of outstanding postmarketing study commitments;
- The number of outstanding study commitments for which no reports were submitted to FDA;
- The number of concluded studies that
    1. satisfied an applicant's commitment;
    2. failed to satisfy an applicant's commitment;
    3. FDA deemed no longer feasible or needed.

To provide public access to information on the status of specific postmarketing studies, FDA will also report detailed information on individual postmarketing study status reports submitted under 21 CFR 314.81(b)(2)(vii) and 601.70 on an agency Internet website. The information included on the Internet website (a representative example of which is provided in Appendix B to this document) will be updated quarterly and will allow patient and consumer groups to follow the progress of specific studies of importance to them. The website will include the following information:

- Name of Applicant;
- Product Name/Proprietary Name(s);
- Route of Administration/Dosage Form/Strength;
- NDA, ANDA, or BLA Application Number and supplemental number if applicable;

[2] "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 C.F.R. 20.61(a).

[3] See, for example, 21 C.F.R. 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."

- Date of US Approval;

- Postmarketing Study Commitment:
  - Commitment Date
  - Type of Study
  - Commitment Description
  - Projected Study Completion Date
  - Current Status of Study
  - Explanation of Study Status

- Annual Report Due Date;

- Date Report Received.

In establishing the FDA website, both CDER and CBER will use data from their electronic databases, to the extent such data have been determined to be reliable, to identify postmarketing study commitments for which a report was expected, but not received. The FDA website will include identification of applicants who failed to submit a status report and describe the unfulfilled commitment(s).

To permit applicants with postmarketing study commitments to more fully participate in the disclosure process, you can submit with your annual report a publicly releasable version of the report that contains the information identified above (including information that may be considered confidential commercial information), edited to the extent necessary to protect trade secrets (see footnote 2) or to conceal individual patient identifiers (see footnote 3). Each page of this copy should be clearly marked **For Public Release**. It is helpful to FDA if you submit such information in an electronic format compatible with FDA's electronic database. Guidance on the electronic submission of information to FDA can be found in:

- *Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations (January 28, 1999);*
- *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format-Biologics Marketing Application (BLA), Product License Application (PLA)/Establishment License Application (ELA) and New Drug Application (NDA) (November 12, 1999, REVISED November 22, 1999).*

Study commitments will continue to be listed on the FDA Internet website for one full year from the date of FDA's letter confirming that the commitment was fulfilled. After that year has passed, all reference to the study will be removed from the website.

APPENDIX A: SAMPLE: POSTMARKETING STATUS REPORT (Submitted by Applicant)

Postmarketing Study Report: 02/01/2000.

Applicant: AABBCC Pharmaceuticals, Inc. **NDA No:** 12-345.
Product: Efficacymycin (Curritt)/Oral, gelatin capsules (25 mg; 50 mg).
U.S. Approval Date: 12/31/97.

Commitment Date: 12/31/97.
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 gelatin capsules.

Original Schedule for Conduct of Study: Final draft protocol will be submitted to 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 FDA by 10/01/00.
Study/Commitment 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.

Commitment Date: 04/01/99 (NDA supplement 12-345/20: 50 mg oral gelatin capsules).
Description of Study Commitment: Evaluate metabolism of Curritt in patients with impaired liver or kidney function who have infections for which Curritt is approved. Study will include approximately 160 patients. Two clinical studies will be performed. Dosage: 50 mg oral gelatin capsules.

Original Schedule for conduct of Study: Two studies are being conducted. Protocols were approved at time of study commitment (04/01/99). Study enrollment will be concluded by 05/01/00. Last patients should complete evaluations by 10/01/00. Study final reports will be submitted to FDA by 02/01/01.
Study/Commitment Status: Delayed.
Explanation of Status: Study in renal impaired patients has concluded with study final report being prepared. Study in hepatic impaired patients has not begun and requires revision to study protocols.

Study #1: 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: Protocol was approved at time of study commitment (04/01/99). Study enrollment will begin by 02/01/00 with enrollment concluded by 05/01/00. Last patients should complete evaluations by 10/01/00. Study final report will be submitted to FDA by 02/01/01.

Revised Schedule: [Revised 02/01/2000]. A revised protocol will be submitted to FDA by 06/01/00. Study enrollment will conclude by 12/01/00. Current study completion date is now anticipated by 06/01/01 with a study final report to FDA by 2/01/02.
Study Status: Delayed.
Explanation of Status: No patients have been enrolled. Two IRBs have raised issues that must be addressed by revising the study protocol.

Study # 2: Evaluation of 50 mg Curritt in patients with impaired renal function. Study to include approximately 60 patients (15 normal).
Original Schedule: Protocol was approved at time of study commitment (04/01/99). Study enrollment will begin by 02/01/00 with enrollment concluded by 05/01/00. Last patients should complete evaluations by 10/01/00. Study final report will be submitted to FDA by 02/01/01.
Study 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 FDA by 02/01/01.

APPENDIX B: SAMPLE: POSTMARKETING STATUS SUMMARY
[To be displayed on FDA Website]

Applicant: AABBCC Pharmaceuticals, Inc.
Product: Efficacymycin (Curritt)/Oral, gelatin capsules (25 mg; 50 mg)
NDA: 12-345.
U.S. Approval Date: 12/31/97.
Annual Report Due Date: 12/31/99.
Annual Report Received: 02/01/00.

Commitment #1:

Commitment Date: 12/31/97.
Study Type: Special Population.
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 gelatin capsules.

Original Projected Completion Date: 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.

Commitment #2:

Commitment Date: 04/01/99.
Study Type: Pharmacokinetic; Special Population.
Commitment: Evaluate metabolism of Curritt in patients with impaired liver or kidney function who have infections for which Curritt is approved. Study will include approximately 160 patients. Two clinical studies will be performed. Dosage: 50 mg oral gelatin capsules.

Original Projected Completion Date: 02/01/01.
Current Status: Delayed.
Explanation of Status: Two studies are being conducted. No patients have been enrolled in the study of impaired liver function. Two IRBs have raised issues that must be addressed by revising the protocol. The current projected study completion date is now 2/01/02. The study in patients with impaired kidney function has concluded with a total of 57 patients enrolled. A study final report is being prepared.