**OFFICE OF NEW DRUGS**

# Procedures for Completing and Processing the Form "Annual Report Review: Postmarketing Study Commitment Summary"

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## PURPOSE

This MAPP describes procedures to be used by Office of New Drug (OND) staff to:

- Verify an applicant's reported status and explanation of status of postmarketing study commitments by completing the form "Annual Report Review: Postmarketing Study Commitment Summary"
- Process the form in the Division File System (DFS)

## BACKGROUND

- Under section 130(a) of Title I of the Food and Drug Administration Modernization Act of 1997 (Modernization Act), the FDA published a final rule on postmarketing study commitments on October 30, 2000 (65 FR 64607). Under the rule, the FDA revised the requirements for annual postmarketing status reports for approved human drug and biological products (21 CFR 314.81(b)(2), 21 CFR 601.70). The rule also described the types of postmarketing studies covered by the status reports, the information to be included in the reports, and the type of information that the FDA would consider appropriate for public disclosure. This rule became effective on April 30, 2001.

- Under the rule, any applicant with a commitment to conduct a postmarketing study for a drug or biological product approved for marketing must submit to the FDA a report on the progress of the study or the reasons the applicant failed to conduct the study. The applicant must submit the report within a year after approval of the product and annually thereafter within 60 days of the anniversary of the product's U.S. approval "until the applicant receives written notification that the agency concludes that: (1) the study commitment has been met, or (2) the study is either no longer feasible or would no longer provide useful information." This provision applies to commitments for postmarketing studies made before or after enactment of the Modernization Act.

- The Agency is obligated under the rule to make publicly available information that pertains to the status of postmarketing study commitments. This is accomplished by obtaining information from outgoing Agency letters and verified annual status reports.

- The Agency has proposed in guidance that we will review an applicant's annual postmarketing study commitment status report within 3 months of receipt to determine whether we agree with the applicant's reported status and explanation of status for each open commitment. The information needed to verify the accuracy of the applicant's reported status and explanation of status for open postmarketing study commitments is captured on the form "Annual Report Review: Postmarketing Study Commitment Summary."

## REFERENCES

- Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), section 130 (Federal Food, Drug, and Cosmetic Act, section 506B)

- Final Rule, "Postmarketing Studies for Approved Human Drug and Licensed Biological Products; Status Reports," 65 FR 64607 (October 30, 2000)

- 21 CFR 314.81(b)(2), Other Postmarketing Reports

- 21 CFR 601.70, Annual Progress Reports of Postmarketing Studies

- FDA draft guidance for industry *Reports on the Status of Postmarketing Studies — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*[1]

## DEFINITIONS

- **Annual report:** A report submitted annually by the applicant within 60 days of the anniversary date of U.S. approval of the application.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

- **CDER Standard Letters System (CSL):** An internally developed application that catalogs and generates standardized letters and forms used by staff in the Center for Drug Evaluation and Research (CDER) new-drug review divisions.

- **Centerwide Oracle-Based Management Information System Personal Edition (COMIS PE):** A tool designed and developed by and for the CDER community to access information in COMIS. COMIS is used by FDA staff to track information about the receipt and review status of investigational new drug applications (INDAs), new drug applications (NDAs), and abbreviated new drug applications (ANDAs).

- **Division File System (DFS):** The document management, tracking, and archiving system used by CDER personnel.

- **Modernization Act:** The Food and Drug Administration Modernization Act of 1997.

- **Postmarketing study commitment (PMC):** Studies that are *required of* or *agreed to by* an applicant and conducted after a product is approved for marketing. Postmarketing studies provide additional information about a product's safety, efficacy, quality, stability, or consistency of manufacture.

- **Status reports of postmarketing study commitments:** A progress report submitted annually for applications with certain open postmarketing study commitments (e.g., clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology studies). For NDAs, the status report is submitted as a section within the annual report; for biologics license applications (BLAs), the annual status report is submitted as a separate report. The report must include all the information required under 21 CFR 314.81(b)(2) and 601.70.

## POLICY

- OND staff will review annual status reports (when submitted for applications with open postmarketing study commitments) and complete the form "Annual Report Review: Postmarketing Study Commitment Summary" to verify the reported status and explanation of status of postmarketing study commitments (see Attachments A and B).

- OND staff will process the form "Annual Report Review: Postmarketing Study Commitment Summary" in DFS within 3 months of FDA receipt of the annual status report (see Attachment B).

## RESPONSIBILITIES AND PROCEDURES

**The OND Project Manager or Division Designee will:**

- Confirm, for applications with open commitments, that the annual status report was submitted and that it addresses all the open commitments established under the application, including supplements (e.g., by comparing the annual status report to a list of open commitments for the referenced application (e.g., COMIS PE report CPE00054)). A list of annual reports received within a specified time frame for applications with open postmarketing study commitments (e.g., COMIS PE report CPE00055) may be used to identify missing status reports.

- Generate a letter to the applicant (letter NDA-N7 in CSL) if the annual postmarketing status report is incomplete or missing as previously determined. [Note: For NDAs, the status of open postmarketing study commitments regarding chemistry, manufacturing, and controls (CMC) may be reported by the applicant in a separate section of the annual report and, therefore, may not necessarily be located in the same section as the other open postmarketing study commitments (e.g., nonclinical, clinical). Therefore, if the status and explanation of status for open CMC commitments are not listed with the other commitments, the project manager or division designee should look elsewhere in the annual report before assuming that the annual status report is incomplete.]

- ***Either*** assume the reviewer responsibilities described in the section "The OND Reviewers will" ***or*** continue with the responsibilities described in the remainder of this section, depending upon the discretionary delegation of responsibilities and roles at the division level.

- Assign the annual report, based on the current reviewer assignments for the application, to the appropriate reviewer or reviewers to include a discipline-specific review of the annual status report of postmarketing study commitments (e.g., chemistry commitments should be assigned to the chemist or product reviewer).

- Ensure that each assigned reviewer promptly receives a copy of the annual status report.

- Collate, as needed, the individual reviewers' assessment of the reported status and explanation of status for open postmarketing study commitments.

- Generate the form "Annual Report Review: Postmarketing Study Commitment Summary" (available in CSL); complete *one* final form based on the collated input received from the assigned reviewer or reviewers; and ensure that all of the open postmarketing commitments reported on by the applicant are accounted for in the completed form. If the annual status report is incomplete, Sections B and C of the form may be used to provide the current status and explanation of status for any open commitments that are not, but should be, listed in the annual status report (see Attachments A and B).

- Contact the applicant if the reported status category and/or explanation of status is/are not supported by adequate information; enter the corrected status and/or explanation of status provided by the reviewer or reviewers in Section C of the form "Annual Report Review: Postmarketing Study Commitment Summary"; and communicate the correction(s) as well as the rationale behind the correction(s) to the applicant (see Attachments A and B). **[Note: If a corrected explanation of status is provided in Section C of the form, be aware that the explanation of status for a delayed or terminated study commitment will be made publicly available on the PMC Web site (www.fda.gov/cder/pmc). Therefore, please ensure that there is no proprietary information (e.g., IND numbers, personal privacy information, or references to unapproved formulations of the same drug or other unapproved drug products) included in the corrected explanation of status.]**

- Process the form "Annual Report Review: Postmarketing Study Commitment Summary" in DFS with the appropriate sign-off (see **AUTHORITY**). The form must be processed in DFS within 3 months of FDA receipt of the annual status report; therefore, the time it takes to review the annual status report, collate comments, generate the form, and process in DFS should be considered in the overall time frame for completion. A list of annual reports received within a specified time frame for applications with open postmarketing study commitments (e.g., COMIS PE report CPE00055) may be used to manage the timely validation of the status reports.

**The OND Reviewers will (if assigned the annual status report for review):**

- Notify the project manager if the status report is incomplete or if any reported status categories are not supported by adequate information. [Note: For NDAs, the status of open postmarketing study commitments regarding chemistry, manufacturing, and controls (CMC) may be reported by the applicant in a separate section of the annual report and, therefore, may not necessarily be located in the same section as the other open postmarketing study commitments (e.g., nonclinical, clinical). Therefore, if the status and explanation of status for open CMC commitments are not listed with the other commitments, reviewers should look elsewhere in the annual report before assuming that the annual status report is incomplete.]

- Review and verify the information provided by the applicant in the annual postmarketing status report regarding the postmarketing study commitments that are specific to the reviewer's discipline. Depending on the number of reviewers involved and the discretionary designation of responsibilities and roles at the division level, the reviewers will also do one of the following:

  – Provide completed comments to the project manager or division designee who will complete and process the form (a formal written review of the annual status report is not required); ***or***

  – Generate and complete the form "Annual Report Review: Postmarketing Study Commitment Summary" (available in CSL) and process in DFS if the reviewer is the sole reviewer *and* the division designee for completing and processing the form. If the annual status report is incomplete, Sections B and C of the form may be used to provide the current status and explanation of status for any open

commitments that are not, but should be, listed in the annual status report (see Attachments A and B).

Only one form should be completed and processed in DFS for each annual status report submitted (i.e., one form per application). The form must be processed in DFS within 3 months of FDA receipt of the annual status report; therefore, the time it takes to review the annual status report, collate comments, generate the form, and process in DFS should be considered in the overall time frame for completion. A list of annual reports received within a specified time frame for applications with open postmarketing study commitments (e.g., COMIS PE report CPE00055) may be used to manage the timely validation of the status reports.

- Do one of the following, upon completion (i.e., sign-off) of the form in DFS, to allow data entry staff immediate access to the annual status report for updating the PMC database:

  – Return the jacketed annual report to the document room *as soon as the verification process is completed* (i.e., by the reviewer completing and processing the form or by sending a review or comments to the person designated to collate, complete, and process the form). If the annual report needs to be returned to the review division, mark the document room's transmittal sheet for the annual report ***Return to _____ (specify name of reviewer)***. **If a review copy of the annual report is returned unmarked to the document room, it will be forwarded to PMC Data Entry, HFD-143, and then shredded.** ***Or***

  – Promptly send a copy of the annual status report for postmarketing study commitments (*not* the entire annual report) that was reviewed to "PMC Data Entry, HFD-143" via interoffice mail and return the jacketed annual report to the document room when convenient. This is the procedure to follow when the reviewer prefers to not return the jacketed annual report to the document room immediately after completion of the validation form (i.e., the reviewer wishes to retain the jacket).

## FORMAT

- See Attachment A.

## AUTHORITY

The form "Annual Report Review: Postmarketing Study Commitment Summary" is completed and processed at the discretion (i.e., responsibilities and roles) of the review division.

## EFFECTIVE DATE

This MAPP is effective upon date of publication.

**Attachment A**

# Annual Report Review: Postmarketing Study Commitment Summary

(This form is solely intended to verify the information provided by applicants in annual status reports for postmarketing study commitments. It should *NOT* be used comparatively against information posted on the Web site or against the information listed in PMC database reports. The form should address all open postmarketing study commitments established under the application(s) whether or not they are subject to posting publicly on the Web site.)

Reviewer:_____ Annual report submitted electronically? ☐ Yes / ☐ No

## SECTION A: Application Information

| | |
|---|---|
| **NDA/ANDA/BLA** | |
| **Drug** | |
| **Applicant** | |
| **Annual Report Number** | |
| **Annual Report Received** | |

## SECTION B: Verification of the Reported Status and Explanation of Status for Open Commitments

| Origin of Commitment (i.e., N-000, S-xxx, or date of post-approval letter if not established at the time of an application's approval) | Commitment # (as numbered in the Agency letter) | Do you agree with the applicant's reported status? (Yes / No / Not Reported) If no, explain in Section C. | Do you agree with the applicant's reported explanation of status? (Yes / No / Not Reported) If no, explain in Section C. |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

## SECTION C: Explanation of Disagreements and Corrections

For each commitment where we do not agree with the applicant's reported status and/or explanation of status, please address the following:

- Explain the disagreement.
- State concisely the correct status and/or explanation of status as it should be reflected in the database and on the Web site. **[Note: The revised explanation of status should not include proprietary information (e.g., IND numbers, personal privacy information, or references to unapproved formulations of the same drug or other unapproved drug products).]**

Supplement # (if appropriate)
Commitment #
Disagreement:
Corrected status and/or explanation of status:
Was the corrected status and/or explanation of status communicated to the applicant? ☐ Yes / ☐ No

Supplement # (if appropriate)
Commitment #
Disagreement:
Corrected status and/or explanation of status:
Was the corrected status and/or explanation of status communicated to the applicant? ☐ Yes / ☐ No

**Attachment B**

# Annual Report Review: Postmarketing Study Commitment Summary Form Instructions for Use

**The form can be found in CDER Standard Letters (CSL) under Forms. This form must be completed for all applications with open postmarketing study commitments (PMCs), including chemistry, manufacturing, and controls (CMCs), reported in the "Status reports of postmarketing study commitments" section of the annual report. You do not need to complete this form for an application's annual report when there are no open commitments for the application.**

**Reviewer:** Enter the name of the person who is completing this form. Names of individual reviewers who contributed comments to complete the form may also be captured here.

**Electronic submission:** Indicate whether or not the annual report was submitted to the electronic document room.

**SECTION A: Application Information**

Provide identifying information including the application number, drug name, applicant name, annual report number (e.g., 011 for Y-011), and receipt date (document room stamp date) in the appropriate fields.

**SECTION B: Verification of the Reported Status and Explanation of Status for Open Commitments**

One *and only one* status should be assigned to each commitment. The status categories for postmarketing study commitments are defined as follows:

***Status Categories***

**Pending:** The study has not begun (i.e., no subjects have been enrolled), but the original projected date for completion of patient accrual has not passed. If patient accrual has started but is not complete, and the projected date for completion has passed, the study should be categorized as *delayed*.

**Ongoing:** The study is proceeding according to, or is ahead of, the original schedule. A study is considered *ongoing* until a final study report is submitted to the FDA, as long as the activities are proceeding according to the original schedule.

**Delayed:** The study is proceeding but is behind the original or final 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 the applicant has one *delayed* phase, but makes up for it in the next phase and gets back on schedule, the *delayed* status will no longer apply.

**Terminated:** The applicant ended the study before completion or does not intend to complete the study as it was originally designed, and the applicant has not yet submitted a final study report to the FDA.

# Annual Report Review: Postmarketing Study Commitment Summary Form Instructions for Use (continued)

**Submitted:** The applicant has completed or terminated the study and has submitted a final study report to the FDA, but the Agency has not yet advised the applicant whether the study commitment has been fulfilled.

**Fulfilled:** The applicant has submitted the final study report for the commitment, and upon review of the final study report, the FDA is satisfied that the applicant has met the terms of the commitment.

**Released:** The FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study.

**Note:** Applicants are not required to report on fulfilled or released PMCs in annual status reports. However, if those commitments are included in the report, any discrepancies in the statuses and/or explanations of status can be captured on this form. Ensure that all the open PMCs reported on by the applicant in its annual status report are accounted for in this section of the form. You may use this section of the form to list open PMCs that were not reported in the annual status report.

**Origin of Commitment:** Identify the source of the FDA's request for the commitment. For example, if the commitment was requested in the original NDA's approval letter, enter *N-000*. If the commitment was requested in an approval letter for supplemental application number xxx, enter *S-xxx*. If the commitment was requested in a separate post-approval letter, enter the date of that letter.

**Commitment #:** Enter the commitment number as it appears in the action or PMC letter from which it originated. Each open postmarketing study commitment reported on in the annual status report should be listed here. The regulations in 21 CFR 314.81(b)(2) and 601.70 do not stipulate that applicants must identify the commitment number according to the number as it appeared in the action letter from which it originated. However, updates to the database rely on identifying PMCs by these numbers relative to the application number. Therefore, please provide the specific PMC numbers in this column even if the applicant did not provide them. A comparison of the annual status report to a list of open commitments for each application (e.g., COMIS PE report CPE00054) can assist you in this task.

**Do you agree with the applicant's reported status?:** Enter *yes*, *no*, or *not reported*.

***Explanation of Status***

**Do you agree with the applicant's reported explanation of status?:** Enter *yes*, *no*, or *not reported*.

The explanation of status is a brief explanation about how the study is progressing in reference to the original projected study schedule. When validating the reported status and explanation of status, be aware that the status of a PMC is based upon the original schedule set forth in the approval letter or the appropriate PMC letter if separate from an approval action. Even if you agree to a revised schedule with the applicant, the applicant must still be held to the original schedule and can be considered *delayed* according to the original schedule. Applicants are likewise instructed in the draft guidance for industry *Reports on the Status of Postmarketing Studies — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*[2] to categorize the status of a commitment according to the original study schedule.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

# Annual Report Review: Postmarketing Study Commitment Summary Form Instructions for Use (continued)

In this section of the form, you may combine into one row all commitments whose statuses *and* explanations of status are accurately reported by the applicant. For example, if commitments 1-5 have all been accurately reported by the applicant (i.e., the statuses *and* explanations of status), you may enter *1-5* on a single row under the "Commitment #" column of this section, followed by *yes* and *yes* under the "Do you agree with the applicant's reported status?/explanation of status?" columns. You should list separately (i.e., one commitment per row) commitments for which you do not agree with the applicant's reported status and/or explanation of status.

Add rows as needed by pressing the *Tab* key from the last field (bottom-right) of the table.

If you have answered *yes* and *yes* under the "Do you agree with the applicant's reported status?/explanation of status?" columns for all of the PMCs listed in Section B, *and* all of the open PMCs have been accounted for in the report and on the form, you are finished completing the form. Process the form in DFS as **Forms; Administrative; Annual Report Review: Postmarketing Study Commitment Summary Form**.

**SECTION C: Explanation of Disagreements and Corrections**

For PMCs listed in Section B where there is disagreement or information was not reported, provide the corrected status (e.g., *only* one of the status categories defined under Section B above) and/or explanation of status in its entirety and the reasons why you disagree with the applicant's reported status and/or explanation in the "Disagreement" section. The corrected status and/or explanation of status as well as the rationale behind the correction(s) should be communicated to the applicant so that it knows how to report the status and/or explanation of status in the next annual status report. Check the appropriate box to indicate whether you have communicated the corrected status and/or explanation of status to the applicant. You may also use this section of the form to provide the correct statuses and explanations of status for open PMCs that were not reported in the annual status report but were listed in Section B of the form.

**Note: If you provide a corrected explanation of status in this section, be aware that the explanation you provide for a delayed or terminated study commitment will be made publicly available on the PMC Web site (www.fda.gov/cder/pmc). Please ensure that there is no proprietary information (e.g., IND numbers, personal privacy information, or references to unapproved formulations of the same drug or other unapproved drug products) included in the corrected explanation of status.**

Add rows as needed by pressing the *Tab* key from the last field (bottom-right) of the table.

**DFS Processing:**

Submit this form into DFS under **Forms; Administrative; Annual Report Review: Postmarketing Study Commitment Summary Form** with sign-off as determined at the division level.

**Contact Information:**

If you have any questions regarding the form or these instructions, please contact Beth Duvall-Miller, Postmarketing Study Commitment Program Coordinator, at duvallmiller@cder.fda.gov or (301) 594-3937.