POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Procedures for Completing and Processing the Form "Annual Status Report Review Form: PMR and PMC Summary"

Table of Contents

PURPOSE

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

  – Verify an applicant's reported status and explanation of status for **postmarketing requirements (PMRs)** and **postmarketing commitments (PMCs)**[1] reportable under section 506B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 356b) that are reported each year in the PMR/PMC **annual status report (ASR)**

  – Complete the form "Annual Status Report Review Form: PMR and PMC Summary" (*ASR Review Form*) and process the form in the electronic document tracking and archiving system

[1] Terms bolded at first use are defined in the Definitions section.

- This MAPP does not apply to PMCs not subject to the reporting requirements of section 506B of the FD&C Act; for example, PMCs related to chemistry, manufacturing, and controls[2]

BACKGROUND

- PMRs/PMCs are studies or clinical trials conducted by the applicant after the Food and Drug Administration (FDA) has approved a drug for marketing or licensing.[3] These studies or clinical trials can be either required by regulation or statute (PMRs) or agreed upon by the FDA and the applicant (PMCs). (See the Definitions section.)

- Section 130(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended the FD&C Act by adding a new provision requiring reports of certain postmarketing studies for human drug and biological products (section 506B of the FD&C Act (21 U.S.C. 356b)).[4] Section 506B of the FD&C Act provides the FDA with additional authority to monitor the progress of a PMR/PMC[5] by requiring the applicant to submit an annual report that provides information on the status (as defined in 21 CFR 314.81) of the PMR/PMC. This report must also include the reasons, if any, for failure to complete the requirement or commitment. This provision is implemented at 21 CFR 314.81(b)(2)(vii) and 601.70. The regulations went into effect on April 30, 2001 (66 FR 10815).

- Effective March 25, 2008, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) created section 505(o) of the FD&C Act, which authorizes the FDA to require certain postmarketing safety studies or clinical trials and requires applicants to submit a timetable for completion of each study or clinical trial. Applicants are also required to report periodically on each

[2] The status of PMCs not subject to the reporting requirements of section 506B of the FD&C Act must be included in a separate section of the new drug application annual report as required under 21 CFR 314.81(b)(2)(viii) or, for biological products, in the annual report of changes to a biologics license application required under 21 CFR 601.12. The appropriate Office of Pharmaceutical Quality reviewer reviews these reports.

[3] For the purposes of this MAPP, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[4] 21 CFR 314.81(b)(2)(vii) and 601.70 refer to studies and clinical trials concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology.

[5] Although reporting under section 506B of the FD&C Act, as required under 21 CFR 314.81(b)(2)(vii), refers only to PMCs, some of these commitments are required under the Pediatric Research Equity Act (21 CFR 314.55(b) and 601.27(b)), the animal efficacy rule (21 CFR 314.610(b)(1) and 601.91(b)(1)), accelerated approval (21 CFR 314.510 and 601.41), and the Food and Drug Administration Amendments Act of 2007 (section 505(o)(3)(A); 21 U.S.C. 355(o)(3)(A)) and are now referred to as PMRs.

safety study or clinical trial required or otherwise undertaken to investigate a safety issue. Submission of the annual report on the status of PMRs/PMCs required under section 506B of the FD&C Act will satisfy the periodic reporting requirements for PMRs under FDAAA as long as all required elements are included.

- The PMR/PMC ASRs required under section 130(a) of FDAMA are due each year within 60 days of the anniversary of the U.S. drug approval or an alternate date formally agreed upon by the FDA (e.g., harmonized annual report due date as granted in the Combined Annual Report Granted letter or the Harmonized Annual Report Due Date Granted letter). The applicant must continue to report on the status of the PMR/PMC until it is notified in writing that the PMR/PMC has been fulfilled or released.[6] This provision applies to requirements and commitments made before or after enactment of FDAMA.

- The FDA reviews the ASRs and then updates the status and other information in the PMR/PMC database.[7] (See Attachment 1, PMR/PMC Status Definitions.) The FDA uses the database to track PMR/PMC status and as a data source for certain information that is displayed on an FDA public website.[8] The FDA also uses the PMR/PMC database as the source for data published annually in the *Federal Register* to meet its obligations for public disclosure of information required under section 506B(b) and (c) of the FD&C Act.

POLICY

- OND staff, in consultation with other review staff as necessary, will review an applicant's ASR within 3 months of receipt to determine whether we agree with the applicant's reported status and explanation of status for each open and **506B-reportable PMR/PMC**.[9] The information needed to document the FDA's concurrence with the applicant's reported status and explanation of status for open PMRs/PMCs will be captured on the ASR Review Form, which may be found in

[6] The applicant must continue to report even after the final report has been submitted until notified by the FDA that the PMR/PMC has been closed (released or fulfilled).

[7] The PMR/PMC database refers to the PMR/PMC information within the electronic document tracking and archiving system used in the Center for Drug Evaluation and Research to capture and track all information related to all drug applications, including information about PMRs/PMCs.

[8] See https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

[9] See the 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*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

the **Center for Drug Evaluation and Research (CDER) Standard Templates** repository. One ASR Review Form will be completed for each ASR submission.

- Each OND review division will verify and document the status and explanation of status of all open 506B-reportable PMRs/PMCs through review of the ASR.

- The **PMR/PMC tracking coordinators**[10] within the OND review divisions will review ASRs submitted for applications with open 506B-reportable PMRs/PMCs.

  – As needed, the PMR/PMC tracking coordinator will obtain information from other review staff to confirm the status of a PMR/PMC (e.g., staff in the Office of Clinical Pharmacology (OCP), Office of Biostatistics (OB), Office of Surveillance and Epidemiology (OSE), or Office of Pharmaceutical Quality (OPQ))

  – The OND safety regulatory project managers (SRPMs) will be responsible for the accuracy and completeness of the ASR Review Form, regardless of who reviewed the ASR and completed the ASR Review Form[11]

RESPONSIBILITIES AND PROCEDURES

The OND Regulatory Project Manager will:

- Confirm, for applications with open PMRs/PMCs, that the ASR was submitted on time and correctly identified (e.g., "Annual Report with PMR/PMC") in the electronic document tracking and archiving system

  – If the new drug application (NDA) ASR is not submitted within 60 days of the due date, issue an Annual Report Requested letter to the applicant

- Notify the division's PMR/PMC tracking coordinator (and OND SRPM, if applicable) that the ASR was received

- Ensure that each reviewer assigned to the application and the PMR/PMC tracking coordinator promptly has access to the ASR submission (e.g., receives a hard copy or link to the electronic file)

[10] PMR/PMC tracking coordinators are members of OND review division staff and are usually OND safety regulatory project managers; however, this varies per review division. See the Definitions section.

[11] See MAPP 6010.2 *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*.

The PMR/PMC Tracking Coordinator will:

- Confirm that the ASR addresses all open and 506B-reportable PMRs/PMCs established under the application, including supplements

  – Compare the PMRs/PMCs included in the ASR to those listed in the electronic document tracking and archiving system to verify that the ASR is complete

  – If the electronic document tracking and archiving system does not reflect accurate and complete PMR/PMC information, contact the document room data entry staff (CDER-OSP-OBI-PMR/PMC) to request the necessary data entry or corrections, as applicable (e.g., if an open reportable PMR or PMC is included in the ASR, but it is not appropriately reflected in the electronic document tracking and archiving system, request that the PMR/PMC be added to the system)

- Issue a PMR/PMC Annual Report Missing or Incomplete letter to the applicant if:[12]

  – The NDA ASR is incomplete (e.g., does not report on all open reportable PMRs/PMCs)

  – The biologics license application (BLA) ASR was not submitted as a stand-alone submission or is incomplete (e.g., does not report on all open PMRs/PMCs)

- Monitor for the applicant's response to any issued PMR/PMC Annual Report Missing or Incomplete letters within the response time frame specified in the letter and consult with the Office of Scientific Investigations if the applicant fails to respond within the specified time frame

- Complete the review of the ASR using the ASR Review Form that is available in the CDER Standard Templates repository (also see Attachment 1, PMR/PMC Status Definitions)

  – As needed, obtain information from other review staff to confirm the status of a PMR/PMC (e.g., staff in OCP, OB, OSE, and OPQ) and complete review of the ASR

[12] Typically the letter should be issued within 60 days of the ASR due date for a missing biologics license application ASR, or within 60 days of receipt of an incomplete ASR.

For ASRs that include PMRs/PMCs required or requested by multiple OND review divisions, the PMR/PMC Tracking Coordinators in each division will:

- Agree upon a *lead*[13] division for review of the ASR

  – The PMR/PMC tracking coordinator in the lead division will review his or her assigned portion of the ASR and if additional reviews of the ASR are conducted by **discipline reviewers** in the various offices and divisions, compile the information into a single ASR Review Form and enter it into the electronic document tracking and archiving system

When ASR review is delegated to someone other than the PMR/PMC Tracking Coordinator, the PMR/PMC Tracking Coordinator will:

- Review the ASR Review Form before uploading the final form into the electronic document tracking and archiving system

The Discipline Reviewer(s) (if applicable) will:

- Review the regulatory status definitions (see Attachment 1, PMR/PMC Status Definitions) and refer to the official timelines for any open reportable discipline-specific PMRs/PMCs under the application in the electronic document tracking and archiving system before reviewing the ASR

- Review and verify in a timely manner the information provided by the applicant in the ASR for PMRs/PMCs specific to the reviewer's discipline

- Notify the division's PMR/PMC tracking coordinator if any reported status is not supported by adequate information or if the extent of progress of the PMR/PMC indicates that discussion with the applicant is necessary (e.g., if the ASR reflects continued challenges in conducting the PMR/PMC).

- Provide discipline-specific input about the status of the PMR/PMC to the division's PMR/PMC tracking coordinator who will complete and process the ASR Review Form

  – A formal written review of the ASR by the collaborating reviewers is not required

[13] The lead division is typically the review division assigned to the original application in the electronic document tracking and archiving system (the *parent* division), unless all PMRs/PMCs requested by that division are already closed. If all PMRs/PMCs requested or required by the parent division are closed, the lead division will be that division with the largest number of open PMRs/PMCs.

The Document Room Data Entry staff will:

- Perform data entry based on the completed ASR Review Form per existing document room standard operating procedures

  – Typically data entry should be performed within 2 weeks of the completed ASR Review Form being archived in the electronic document tracking and archiving system

- Contact the author for clarification if there are any questions regarding the content of the ASR Review Form

REFERENCES

- Federal Food, Drug, and Cosmetic Act, section 506B (https://legcounsel.house.gov/Comps/Federal%20Food,%20Drug,%20And%20Cosmetic%20Act.pdf), and section 505(o)(3), created by section 901 of FDAAA (https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm)

- 21 CFR 314.81(b)(2), Other postmarketing reports

- 21 CFR 601.12, Changes to an approved application

- 21 CFR 601.70, Annual progress reports of postmarketing studies

- Guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

- 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* (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

- MAPP 6010.2 Rev. 1 *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments* (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

- MAPP 6010.9 *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments* (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm)

DEFINITIONS

- **506B-reportable PMRs/PMCs** — Postmarketing studies or clinical trials concerning clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology that applicants have agreed upon in writing or are required to conduct.[14] Section 130 of FDAMA requires applicants to submit ASRs. The FDA is then required to make publicly available certain information about these studies or clinical trials.

- **Annual status reports (ASRs) of PMRs and PMCs** — A progress report submitted each year for applications with certain open PMRs and PMCs (e.g., clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology studies and clinical trials). For NDAs, the ASR is submitted as a section within the annual report required for the application under 21 CFR 314.81(b)(2)(vii); for BLAs, the ASR is submitted as a separate report. This separate report must include all the information required under 21 CFR 314.81(b)(2) and 601.70. See also the definition of PMRs and PMCs that are reportable under section 506B.

- **Center for Drug Evaluation and Research (CDER) Standard Templates** — A collection of internally developed templates used by CDER staff in new drug review divisions to generate standardized letters and forms.

- **Discipline reviewers** — The FDA reviewers assigned to an application who specialize in and conduct a specific scientific review (e.g., clinical, clinical pharmacology, nonclinical toxicology, safety-related disciplines, quality, biostatistics).

[14] 506B reporting is described as PMCs, even though some of these commitments are required under the Pediatric Research Equity Act, 21 CFR part 314, subparts H and I, and 21 CFR part 601, subpart E. Similarly, this reporting often refers to a study; FDAAA distinguishes between study and clinical trial. Finally, 506B reporting includes clinical safety PMCs; studies or clinical trials that concern serious safety risks are required under FDAAA.

- **PMR/PMC tracking coordinator** — One or more OND review division staff members, generally an OND SRPM, with the role of ensuring that the review team is kept informed of PMR/PMC schedule milestones,[15] verifying PMR/PMC information for accuracy, completing the ASR Review Form, and monitoring whether expected activities are conducted according to the timelines specified in the approval letter or Acknowledge New PMR/PMC letter (after approval) and in CDER policy documents (e.g., applicant submissions and FDA review). The PMR/PMC tracking coordinator's responsibilities generally occur after approval.

- **Postmarketing commitment (PMC)** — Any study or clinical trial that an applicant has *agreed*, in writing, to conduct after approval of a marketing or licensing application or supplement that is *not* a PMR (see below).

- **Postmarketing requirement (PMR)** — Any study or clinical trial that an applicant is required to conduct after approval of a marketing or licensing application or a supplement. Studies or clinical trials may be required under the Pediatric Research Equity Act (21 CFR 314.55(b) and 601.27(b)), the animal efficacy rule (21 CFR 314.610(b)(1) and 601.91(b)(1)), accelerated approval (21 CFR 314.510 and 601.41),[16] or FDAAA (section 505(o)(3)(A); 21 U.S.C. 355(o)(3)(A)).

SUMMARY OF CHANGES

- This MAPP was revised to clarify the policies, responsibilities, and procedures for the completion of the ASR Review Form, and to add Attachment 1, PMR/PMC Status Definitions.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

[15] PMR/PMC schedule milestones are the specific milestone dates set forth as part of a PMR/PMC for conducting and completing a PMR/PMC that must be reported annually. The following milestone dates should be included in the schedule: draft protocol submission date, final protocol submission date, study or clinical trial completion date, and final report submission date.

[16] The PMRs an applicant is required to conduct under 21 CFR 314.510 and 601.41 are referred to as *confirmatory trials* per the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
3/16/05	Initial	n/a
10/26/11	Rev. 1	Removes references to outdated data management and letter template systems; includes additional background information describing the FDA's new authority to require postmarketing safety studies and clinical trials under section 505(o) of the FD&C Act; reflects the new PMR terminology; adds new references relevant to PMR/PMC tracking; updates the ASR Review Form and instructions to more clearly capture PMR/PMC information.
09/27/2017	Rev. 2	Clarifies the roles and responsibilities, removes references to outdated information, and replaces the ASR Review Form and Instructions for Use attachments with a list of PMR/PMC status definitions.

Attachment 1: PMR/PMC Status Definitions

The following status definitions have been adapted from 21 CFR 314.81 and 21 CFR 601.70.

- **Pending** — The study or clinical trial has not been initiated, but does not meet the criterion for delayed

- **Ongoing** — The study or clinical trial is proceeding according to or ahead of the original schedule[17]

- **Submitted** — The study or clinical trial has been completed or terminated and a final report has been submitted to the FDA

- **Delayed** — The study or clinical trial is behind the original schedule[18]

- **Terminated** — The study or clinical trial was ended before completion but a final report has not been submitted to the FDA

- **Fulfilled** — The final report for the study or clinical trial was submitted to and reviewed by the FDA, and the FDA notified the applicant through written correspondence that the requirement or commitment was fulfilled

- **Released** — The FDA has informed the applicant in writing that it is released from its obligation to conduct the study or clinical trial because the study or clinical trial is no longer feasible, would no longer provide useful information, or the underlying application has been formally withdrawn (in the *Federal Register*)

- **Open** — Postmarketing requirement/postmarketing commitment (PMR/PMC) status of pending, ongoing, delayed, submitted, or terminated

- **Closed** — PMR/PMC status of released or fulfilled

[17] 21 CFR 314.81 and 21 CFR 601.70 specify the *original schedule* as the reference point for determining postmarketing requirement/postmarketing commitment status.

[18] Section 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the Food and Drug Administration Safety and Innovation Act of 2012, authorizes the FDA to grant an extension of deferral of pediatric assessments that are required under the Pediatric Research Equity Act if certain applicable Pediatric Research Equity Act criteria for deferral are met and the applicant submits certain materials in support of the extension. Granting of a deferral extension by the FDA results in the original final report due date being replaced with the extended deferral date (final report due date).