SOPP 8413: Postmarketing Requirement/Commitment Related Submissions - Administrative Handling, Review, and CBER Reporting

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff to administratively process, review submissions and report on postmarketing requirements (PMRs) and postmarketing commitments (PMCs) received in CBER for Biological License Applications (BLAs) and New Drug Applications (NDAs).

II. Scope

A. This SOPP applies to *all* PMRs and PMCs for licensed biologics (including devices approved under a BLA) and drugs approved under an NDA regulated by CBER. See *Appendix A: Table 1: Requirements for the Categories of PMRs/PMCs* for additional information.

B. This SOPP does not apply to any device post approval requirements in a Premarket Approval Application (PMA) or to postmarketing studies conducted on an applicant's own initiative (i.e., voluntary studies).

C. This SOPP does not discuss policy and procedures for PMR/PMC development or data entry into RMS-BLA. These topics are described in *SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments*, and the *RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions* internally available in RMS-BLA

D. This SOPP does not address the processing for milestone schedule changes related to Food and Drug Administration Amendments Act of 2007 (FDAAA) Title IX PMRs or Pediatric Research Equity Act (PREA) PMRs and updated in Section 505B of Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. Processing of safety-related good cause issues are described in *JA 860.04: FDAAA PMR Safety-Related Good Cause Issues* and deferral extension requests are described in *JA 860.08: Instructions for Processing Deferral Extension Requests from the Applicant for Pediatric Postmarketing Requirements (PMR).* Also refer to *SOPP 8421: Complying with Requirements under the Pediatric Research Equity Act (PREA).* Applicants having questions or concerns regarding meeting required milestones for PREA PMRs and FDAAA Title IX PMRs should contact the assigned RPM to receive instructions for submitting either a PREA Deferral Extension request or a Request for Good Cause Determination (i.e., "Notification of Failure to Meet a PMR Milestone(s) Required Under Section 505(o)) under FDAAA Title IX.")

III. Background

A. PMRs/PMCs are studies or clinical trials that are conducted by the applicant after the Food and Drug Administration (FDA) has approved or licensed a product for marketing. These studies or clinical trials can be either required by regulation or statute (PMR), or agreed upon, in writing, between FDA and the applicant (PMC).

B. The Food and Drug Administration Modernization Act of 1997 (Modernization Act) contained new requirements for FDA and applicants with regard to postmarketing studies.

1. Section 506B, *Reports of Postmarketing Studies*, requires applicants that have agreed to conduct a postmarketing study to submit annual reports to the FDA on the status of the PMC until the applicant is notified in writing that the commitment has been fulfilled or that they have been released from the commitment.

2. FDA's *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*, describes in detail the content, format and timing of the annual report required by section 506B of

the FD&C Act and the reporting of other postmarketing studies not subject to section 506B.

3. In implementing Section 506B, 21 CFR 314.81(b)(2)(vii) (NDA annual report), 21 CFR 601.28 (biologics licensing, annual reports of postmarketing pediatric studies); and 21 CFR 601.70 (annual progress reports of postmarketing studies for biologics) were revised. The requirements for annual reporting under 21 CFR 601.70 are limited to PMRs and 506B PMCs.

C. Section 901 of Food and Drug Administration Amendments Act (FDAAA) created section 505(o) of the FD&C Act, which authorizes the FDA to require postmarketing studies or clinical trials at the time of approval or after approval if the FDA becomes aware of "new safety information."

1. FDAAA section 505(o)(3)(B) states that the FDA has the authority to require certain postmarketing safety studies or clinical trials, and to require applicants to submit a milestone schedule for completing each study or clinical trial.

2. In addition, FDA has the authority to enforce these requirements for postmarketing studies and clinical trials under FDAAA Section 505(o)(3)(E)(ii). Violations include the applicant's failure to comply with the timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) unless the applicant demonstrates good cause for the noncompliance or violation. The FDA will determine what constitutes good cause.

D. All PMRs and 506B PMCs are annually reported in the *Federal Register* and quarterly on FDA's Postmarket Requirements and Commitments web page. FDA reports on the compliance of applicants with regard to PMR/PMC submissions as required by the FD&C Act. The applicant and FDA reporting requirements are detailed in the FDA's *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*.

E. The Food and Drug Omnibus Reform Act of 2022 (FDORA) amended section 506 of the Federal Food, Drug, and Cosmetic Act (FDCA) to require applicants of products granted accelerated approval to submit two accelerated approval (AA) PMR Progress Reports per year on the status of any open study or clinical trial AA PMR. Each year:

1. One report will be due 180 days after the original date of approval (with a 60-day grace period).

2. A second report, also called a 180-day report, is to be submitted with the applicant's PMR/PMC annual report (see 21 CFR 314.81(b)(2) for NDAs or 21 CFR 601.70 for BLAs).

F. FDORA provides FDA with an expedited withdrawal procedure for drugs/biologics (or indications) approved through accelerated approval that fail to complete required studies or if such studies do not confirm benefit.

IV. Definitions

A. 506B Annual Reports – Annual status updates of PMRs or 506B PMCs provided under 21 CFR 314.81(b)(2)(vii) or 21 CFR 601.70.

B. 506B-Reportable Postmarketing Commitment (506B PMC) – Postmarketing studies or clinical trials concerning clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology that applicants and the FDA have *agreed* to conduct in writing; and applicants are required to report on these PMCs in their PMR/PMC annual report (21 CFR 314.81(b)(2)(vii)(a), 21 CFR 601.70(b), and Section 506B the FD&C Act, *Reports of Postmarketing Studies*).

C. Clinical Trial – Any prospective investigation in which an applicant or investigator determines the method of assigning the investigational product or other interventions to one or more human subjects.

D. Non-506B, Non-Reportable, Postmarketing Commitments (non-506B PMC) – Any Chemistry, Manufacturing, and Control (CMC) study, *agreed* to be conducted in writing (i.e., in an approval or other letter), to assess drug or biologic product quality data that was not required for approval; yet the review committee felt was necessary to provide complete quality information. These commitments are not subject to 506B's reporting requirements.

E. PMR/PMC- Related Submission – A formal applicant submission intended to address an established PMR or PMC. **NOTE**: See *Appendix A: Table 2: Identification of a PMR/PMC Related Submission to an IND, BLA or NDA* for additional information.

F. PMR/PMC Status Types (adapted from 21 CFR 314.81 and 21 CFR 601.70):

1. **Pending**: The study of clinical trial has not been initiated but does not meet the criterion for delayed.
2. **Ongoing**: The study or clinical trial is proceeding according to or ahead of the original schedule.
3. **Submitted**: The study or clinical trial has been completed or terminated and a final report has been submitted to the FDA.
4. **Delayed**: The study or clinical trial is behind the original schedule.

5. **Terminated**: The study or clinical trial was ended before completion, but a final report has not been submitted to the FDA.
6. **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.
7. **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 (license revoked for a BLA or in the Federal Register for an NDA)

G. PMR/PMC Annual Report Review Form (PARRF) – used to review the PMR/PMC Annual Reports for 505(o) and 506B reportable PMRs/PMCs to determine whether the information on the study status and the explanation of status provided by the applicant are appropriate, ensure that the study is proceeding in accordance with the original schedule, and summarize the explanation of status provided by the applicant.

H. PMR/PMC Schedule Milestones – The specific study dates for completing activities related to conducting a PMR/PMC.

I. Postmarketing Commitment (PMC) – Any study or clinical trial that an applicant has *agreed upon*, in writing, to conduct after approval or licensing of a marketing application or supplement that is not a PMR.

J. 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), or FDAAA/Title IX (section 505(o)(3)(A); 21 U.S.C. 355(o)(3)(A)). **NOTE**: Applicants may be subject to FDA enforcement actions for not conducting PMRs.

K. Study – Any investigation other than a clinical trial, such as an investigation in humans (e.g., an observational epidemiologic study), an animal study, or a laboratory experiment.

L. Voluntary Postmarketing Study or Trial – A study or clinical trial conducted on an applicant's *own initiative* without a request by FDA and is not a 506B reportable PMR or PMC.

M. "Safety-related" Study (Title IX PMR under FDAAA or 506B safety-related PMC) - A study being conducted specifically to evaluate safety or further

investigate a safety issue(s) associated with a product. **NOTE:** A study must have a primary safety endpoint to be considered a safety-related study.

N. "Safety-related Product Quality Study PMR" (Title IX PMR under FDAAA)- A quality (CMC) study conducted specifically to address unresolved product quality issues related to the risk of a serious adverse drug experience under FDAAA. NOTE: A study must have a primary endpoint related to product quality safety to be considered a safety-related product quality study. For example, in order to identify a serious risk of patient exposure to a virus and subsequent viral infection, a safety-related product quality study may be required to demonstrate clearance or inactivation of viruses.

O. Off-schedule PMR/PMC – Open PMRs/PMCs that have missed one of the milestone dates in the original schedule and are categorized as either delayed or terminated.

P. 180-Day AA PMR Progress Report - Applicants must submit a "180-day report" twice per year if there are open AA PMRs. There is a standalone 180-day report submission and a subsequent 180-day report that will be combined with the PMR/PMC annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70.

V. Policy

A. CBER will:

1. Accurately track and manage PMR- and PMC-related submissions to ensure closure of the PMR or PMC

NOTE: *RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions* is a document that provides more detailed instructions on entering and updating RMS-BLA.

2. Review PMR- and PMC-related submissions according to the following timeframes:

a. Clinical Protocols – Under the IND, CBER will conduct a timely review of all PMR/PMC protocols submitted by the applicant. CBER will provide detailed feedback to the sponsor/applicant on noted deficiencies and suggested revisions if there are concerns with the submitted protocol design. Protocols do not have specific review timeframes; however, submission of a final protocol can be tracked PMR/PMC milestone.

b. Annual Reports – If CBER does not agree with an applicant's categorization of the status and/or explanation of status of the PMR/506B PMC, CBER will contact the applicant for resolution.

i. **PMR/PMC Annual Report** (may contain 180-day AA PMR Progress Report if required)– used for BLA annual reports (21 CFR 601.70) for reportable PMRs/PMCs: **Reviewed on a 3-month timeframe**.

ii. **Changes to an Application/PMC Annual Report** (may contain 180-day AA PMR Progress Report if required) used for NDA annual reports (21 CFR 314.81(b)(2)(vii)) including reportable PMRs/PMCs: **Reviewed on a 3-month timeframe**.

c. **180-Day AA PMR Progress Report**– used to report status of open AA PMRs: **Reviewed on a 90-day clock**

d. **Final Reports** – CBER will review a Final Study Report, submitted as a supplemental application, according to established review times for supplements (e.g., for User Fee Act (PDUFA) products). CBER will notify the applicant in writing of CBER's determination with regard to the status of the PMR or PMC, i.e., fulfillment or release.

i. Final Study Report – PMR/PMC Submission/Final Study Report: **Reviewed on a 12-month timeframe**;

ii. Final Study Report – BLA/NDA Supplement:

a) Standard Efficacy: **Reviewed on a 10-month timeframe**.

b) Priority Efficacy: **Reviewed on a 6-month timeframe**.

c) Manufacturing Prior Approval: **Reviewed on 4-month timeframe**.

d) Labeling Prior Approval: **Reviewed on 6-month timeframe**.

e) Changes Being Effected (CBE) or CBE-30: **Reviewed on 6-month timeframe**.

d. **PREA PMR Deferral Extension Request**: required for applicants to request additional time to complete outstanding PREA PMRs. Must be submitted as a PMR/PMC Submission/Deferral Extension Request submission, to the BLA/NDA no later than 90 days prior to the Final Study Report due date. **Reviewed on a 45-day timeframe.**

e. **PMR Release Request** – CBER will review and provide a decision on an applicant's request to release (or release/replace) a PMR within 60

days of receipt of the original request or within 60 days of receipt of the additional information requested by FDA, whichever is later.

Note: CBER will use the CBER Safety Working Group (SWG) to discuss any requested/proposed release (or release/replace) of a Title IX, Accelerated Approval, or Animal Rule PMR. CBER will use the Pediatric Review Committee (PeRC) or Oncology subcommittee of PeRC to discuss any requested/proposed release (or release/replace) of a PREA PMR.

3. The appropriate reviewer will notify CBER's Office of Compliance and Biologics Quality (OCBQ) of an applicant's failure to comply with the requirements of section 505(o)(3)(E)(ii), e.g., milestone schedule for completion, and periodic report submissions.

B. Applicants are required to submit their 506B Annual Reports to the FDA within 60 days after the anniversary of U.S. product approvals (or an alternate date formally agreed upon by the FDA) until the FDA notifies the applicant in writing that all PMRs and 506B PMCs have been fulfilled or released. Further, Section 506B requires the FDA to publish annually in the *Federal Register* information on the compliance of the applicants with this reporting requirement.

C. The new AA PMR reporting requirements apply to any **OPEN** (ongoing, pending, delayed status) AA PMRs imposed on the Applicant pre- and post-FDORA.

D. Section 506B of the FD&C Act describes the different PMR/PMC status types which an applicant is required to use in their 506B Annual Report. (See *Final Rule, "Postmarketing Studies for Approved Human Drugs and Licensed Biological Products; Status Reports*," 65 FR 64607 (October 30, 2000) or *R 860.03: Definitions for PMR/PMC Status Types* for status definitions):

1. Open Status Types:

a. On Schedule
- **i.** Pending
- **ii.** Ongoing
- **iii.** Submitted

b. Off Schedule
- **i.** Delayed
- **ii.** Terminated

2. Closed Status Types:
a. Fulfilled

b. Released

D. The milestone schedule for a FDAAA Title IX PMR is a set of dates to measure the progress of the study and clinical trial and assess compliance with FDAAA requirements. FDAAA does not include provisions to amend or change the original milestone dates for purposes of reporting as required under 21 CFR 314.81(b)(2)(vii)(a)(8) and 21 CFR 601.70(b)(8). Therefore, status reporting under these regulations will remain based on the *original* schedule located in the approval letter even if FDA has determined an applicant's good cause for missing a milestone was made.

E. Submissions related to PMRs/PMCs may be made to an Investigational New Drug Application (IND) or BLA/NDA (application), depending on the type of PMR/PMC submission.

1. Submissions made to the IND:

a. A new or revised clinical protocol.

2. Submissions made to the BLA or NDA:

a. A cross-reference letter to the application providing notification that a new or revised protocol has been submitted to the IND.

b. 506B Annual Reports of Open Reportable PMRs/PMCs are submitted:

i. As a separate stand-alone report to the BLA (21 CFR 601.70(b)(8)) or
ii. As a section in the required annual report to the NDA (21 CFR 314.81(b)(2)(vii)(a)).

c. Milestone schedule changes (e.g., PREA Deferral Extension Requests for PREA PMRs, Good Cause Requests for FDAAA Title IX PMRs).

d. Changes to the text, content, or intent of a PMR/PMC.

e. Requests to be released from a PMR/PMC.

f. Final Study Reports

g. Supplements containing Final Study Reports.

NOTE: Any labeling changes (applicant or FDA requested) to fulfill a PMR or PMC must be approved under a labeling or efficacy supplement.

VI. Responsibilities

A. Center PMR/PMC Liaison

1. Serves as the internal Center point of contact to address any questions associated with the development, tracking, or closing of reportable PMRs/PMCs.

2. Prior to letter issuance, reviews all letters containing newly created reportable PMRs/PMCs, letters regarding status updates/changes to reportable PMRs/PMCs, and fulfillment/release letters for all PMCs and PMRs.

B. Lead Reviewer

1. Conducts primary review of 506B Annual Reports, documents review on the PMR/PMC Annual Report Review Form (PARRF), compiles comments from other reviewers and finalizes the PARRF. (See Appendix A, *Table 3: Primary review discipline and regulatory project management for safety-related study* for additional information.)

    a. Office of Biostatistics and Pharmacovigilance/Division of Pharmacovigilance (OBPV/DPV) serves as Lead Reviewer if **ALL** open PMRs or PMCs were safety-related studies with the following study designs: observational epidemiology study, pregnancy registry, study using population-based data sources, survey. The product office will review clinical trials. (Note: this excludes any safety-related product quality PMR).

    b. The product office serves as Lead reviewer if at least one open PMR is for Accelerated Approval, PREA, Animal Rule, a safety-related product quality PMR, a safety-related clinical trial, or is a clinical efficacy PMC.

C. Office Director/ Division Director and/or Branch Chief

1. Ensures staff are aware of and adhere to the procedures for tracking and reviewing PMR/PMC related submissions.

2. Identifies product or clinical Review Committee Member(s) for each PMR/PMC related submission.

3. Participates in discussions and decisions determining whether a PMR or PMC is fulfilled or released.

4. Ensures that review goals for PMR/PMC submissions are met.

5. Ensures that quarterly status reports are accurate and complete.

6. Product Office Division Director or designee serves as the signatory for sponsor letters (if applicable) for PMR/PMC related submissions (see Table 3 in Appendix A).

D. Office PMR/PMC Coordinator

1. Responsible for entering new PMRs/PMCs, tracking PMRs/PMCs, and updating the PMR/PMC tracking system.

2. Provides input and acts as a resource for policy issues related to PMR/PMC tracking and closure.

3. Ensures that the data in the PMR/PMC tracking system are accurate and complete.

4. Actively monitors and provides support to RPMs/Review Committee Members.

5. Drafts and issues "PMC-Annual Report Request" letter for past due annual reports.

6. Monitors due dates to ensure that review(s) of the submission are performed and documented within established timeframes (if any).

7. Uses the *RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions* for detailed instructions on entering and updating RMS-BLA.

E. Product Office Branch/Lab Chief

1. Ensures staff are aware of and adhere to the procedures for tracking and reviewing PMR/PMC related submissions.

2. Provides information and support to the Office PMR/PMC Coordinator.

F. Regulatory Project Manager (RPM) (See Appendix A, *Table 3: Primary review discipline and regulatory project management for safety-related study* for additional information.)

1. Responsible for managing the review based on the PMR/PMC submission.

2. Informs the Office PMR/PMC Coordinators of pending PMRs or PMCs submissions, correspondence, etc.

3. Uses the *RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions* for detailed instructions on entering and updating RMS-BLA.

4. Ensures that any proposed milestone changes to PREA PMRs are scheduled and presented to FDA's Pediatric Review Committee (PeRC). Ensures that applicants submit these changes as Deferral Extension requests.

5. Ensures that any missed milestone changes to Title IX PMRs are classified as "good cause requests" for review and presented to the CBER Safety Working Group (SWG).

G. Office of Operations (ORO), Division of Informatics (DI), Regulatory Information Branch (RIB)

1. Ensures that all necessary tracking elements, reports and functionality for PMR/PMCs are available in RMS-BLA.

2. Makes PMR/PMC reports available (e.g., missing data, status, etc.) to all appropriate parties.

3. Prepares the PMR and 506B PMC data for annual *Federal Register* notice and quarterly for posting on the FDA's Postmarket Requirements and Commitments Web site.

H. Review Committee Member

1. Conducts a technical, scientific, pharmacovigilance, or clinical review of the submission within the stated review timeframes.

2. Consults with appropriate Branch/Lab Chief and Office/Division Directors to determine whether a PMR/PMC should be fulfilled or released.

3. Documents review in a review memo.

I. CBER SWG Representative in Relevant Product Office and OBPV

1. Facilitates communication between the review team and the CBER SWG regarding Title IX PMRs or Safety PMCs.

2. Serves as an office resource on questions related to FDAAA safety provisions.

J. CBER SWG Executive Secretary

1. Manages and schedules the CBER SWG Meeting.

K. CBER Safety Working Group

1. Oversees consistent implementation of procedures associated with Title IX PMRs (such as: good cause or sufficient justification requests for milestone issues) or 506B safety related PMCs as well as requests to release, modify, or fulfill a Title IX PMRs or 506B safety related PMCs.

VII. Procedures

A. General Processing, Receipt and Routing of a PMR/PMC-Related Submission

(See Appendix A, *Table 3: Primary review discipline and regulatory project management for safety-related study* for additional information.) **NOTE:** See section E below for specific procedures for each PMR/PMC submission type. CBER's Document Control Room [DCC] will receive, digitally image (if applicable), process and load submissions into the CBER's Electronic Repository (CER) and notify the appropriate Office through the load notification.

1. Enter submission characteristics into RMS-BLA. **[RPM]**

2. Request/verify reviewer assignments from Branch Chiefs or Division Directors. **[RPM]**

   a. Review the "Reviewers" tab under the PMR/PMC screen in RMS-BLA to help identify the responsible review division and the Office PMR/PMC Coordinator.

   b. Ensure that if the submission pertains to an epidemiologic safety-related study (e.g., observational study, registry, or survey) or a Title IX "good cause" justification for missed milestone, contact the OBPV/DPV Division Director and OBPV/DPV-RPM for review assignments.

3. Determine Review Committee Members for the submission and inform the RPM. **[Division Director, OBPV/DPV Division Director or OBPV/DPV-RPM]**

4. Enter Review Committee Members and Office PMR/PMC Coordinator into RMS-BLA, notify and route (i.e., provide electronic link) to assigned review committee members (including the Office PMR/PMC Coordinator). **[RPM]**

B. General Review Procedures for a PMR/PMC Submission

1. Ensure that the submission is complete. If the submission is incomplete, alert the RPM and request that the RPM contact the applicant to obtain the missing information. **[Review Committee Member]**

2. Contact the applicant to submit an amendment containing the missing information. **[RPM]**

3. Identify the need for and request consults, as needed, from other FDA centers according to *SOPP 8001.5: Inter-Center Consultative Review Process*. **[Review Committee Member, RPM]**

4. Perform review within documented review timeframes per the Policy section.A.5. above. For submissions without agreed-upon timeframes, coordinate agreed-upon timeframe for completing the review of PMR/PMC-related submission. **[Review Committee Member**, **RPM]**

    a. **NOTE**: Modifications to the labeling are required if new safety information triggers a FDAAA Safety Labeling Change (under section 901 (505(o)(4))). Modifications to the label may be requested based on the results of an accelerated approval PMR or a reportable PMC yet should not hold up the review decision.

5. Ensure that the appropriate division(s) and/or office(s) have been consulted for evaluation and review, and that the recommendations have been addressed and/or incorporated into the review. **[Branch/ Lab Chief]**

6. Send any content-related questions or deficiencies, except for protocol related negotiations, to the RPM for communication to the applicant. **[Review Committee Member] NOTE:** Protocol related negotiations and discussions are performed under the IND.

7. Issue an information request as needed to facilitate the review per *SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Submissions* and send a courtesy copy to appropriate review personnel when any such correspondence is sent. **[RPM]**

8. Characterize the amendment and notify and route (i.e., provide electronic link) appropriate Review Committee Members when received. **[RPM]**

9. Participate in discussions and decisions to determine final resolution of the submission, such as, consider whether the submission would fulfill a PMR/PMC or is an applicant request to release (release/replace) a PMR/PMC. **[Branch/ Lab Chief, Office Director/Division Director, Office SWG Representative, CBER SWG for Title IX PMRs or Safety PMCs]**

    Note: The CBER SWG will be used to discuss an applicant's PMR release request for any Accelerated Approval, Title IX, or Animal Rule PMR while the Pediatric Review Committee (PeRC) or the

Oncology subcommittee of PeRC will be used to discuss an applicant's release request for a PREA PMR.

a. Notify the CBER SWG Executive Secretary of the CBER SWG for scheduling any needed discussion of a FDAAA PMR or safety-related 506B PMC at the CBER SWG **[Office SWG Representative]**

10. Provide RPM and Office PMR/PMC Coordinator with an update on the status of the review when asked. **[Review Committee Member]**

11. Document all reviews in writing, incorporate any consultant's recommendations into the discipline review memo and include any letter ready comments and send to the Branch / Lab Chief for secondary review. Ensure that the discipline review memo includes the determination as to the status of the PMR/PMC. **[Review Committee Member]**

a. **NOTE**: For any interim reports the PMR/PMC status should be **ongoing**, **pending**, **submitted**, **terminated** or **delayed**. For Final Study Reports the PMR/PMC status should be **fulfilled** or **released**.

i. PREA PMRs are **not** fulfilled with Final Study Reports. PREA requires the results of all pediatric studies be in the label; therefore, a labeling or efficacy supplement is required as a condition of fulfillment. PREA PMRs will remain in "submitted" status until such a supplement is received and acted upon.

12. Perform secondary reviews. Ensure that the determination of whether the PMR/PMC is fulfilled or released is clearly visible in the review memo. **[Branch/ Lab Chief]**

13. Inform the Product Office or OBPV/DPV RPM and Office PMR/PMC Coordinator of completed reviews. **[Review Committee Member]**

14. Ensure any necessary reviews are completed and uploaded to the appropriate system and issue PMR/PMC tracking-related correspondence to the applicant using the appropriate Review Letter Template (located on CBER's SharePoint page). **[RPM]**

15. Ensure that all appropriate fields within RMS-BLA are populated, including PMR/PMC tracking. **[Office PMR/PMC Coordinator]**

C. Specific Processing Procedures for Different PMR/PMC Submission Types

1. **PMR/PMC Study Protocol**

   a. Ensure that the cross-reference letter is submitted to the BLA/NDA as a PMR/PMC Submission/Correspondence Status Update and the protocol is submitted to the IND. **[RPM]**

   b. Close the cross-reference letter submission according to *JA 833.03: Instructions for Administratively Closing a Submission in RMS-BLA When a Written Review is not necessary* and notify the Office PMR/PMC Coordinator. **[RPM]**

   c. Define the milestone schedule when the approval or notification letter does not contain actual dates, but has a schedule based on a reference to the protocol agreement date. An example is "Protocol submitted: within 6 months after approval." **[Review Committee Member, Branch/Lab Chief]**

   d. Issue the "PMC - Study Schedule Notification Letter" when the milestone schedule is developed with reference to the protocol agreement date and notify the Office PMR/PMC Coordinator. **[RPM]**

      i. **NOTE**: Use this letter only if the approval or notification letter did not include actual dates, yet referred to dates contingent upon the protocol agreement date

   e. Ensure that RMS-BLA contains the IND number and any defined milestone schedule dates. **[Office PMR/PMC Coordinator]**

2. **506B Annual Reports (with or without a 180-day AA PMR report)**

   a. Ensure that the 506B Annual Report is complete (contains updates on all open PMRs and 506B PMCs). Refer to *Appendix B: Reviewer considerations for 506B Annual Reports* for details on the information expected in the 506B Annual Report. **[RPM]**

      i. If the Annual Report contains updates on non-506B (CMC) PMCs, request that the applicant submit non-506B PMC status updates for BLAs as a PMR/PMC Submission - Correspondence Status Update. If the Annual Report contains requests for PMR deferral extensions, or Title IX PMR good cause justifications for a missed milestone, contact the applicant to resubmit those under separate correspondence. **[RPM] NOTE**: For NDAs, updates on non-506B PMC should be included in a separate section of the NDA annual report.

ii. If the Annual Report is not complete, issue the "PMC-Incomplete Annual Report Letter" to the applicant and notify the Office PMR/PMC Coordinator. **[RPM]**

NOTE: If the amendment containing the incomplete annual report information is received before the review due date contact ORO\DIIT\RIB to extend the review due date by 90 days. If the amendment containing the incomplete annual report information is not received before the review due document the incomplete information on the update the submission type in RMS-BLA to "PMR/PMC Submission-Correspondence Status Update" and contact the applicant to resubmit the Annual Report in its entirety.

b. Determine if PMRs/PMCs contained in the 506B Annual Report are only safety-related studies. Consult with OBPV/DPV RPM as necessary. If yes, contact the OBPV/DPV RPM to provide assignment for a OBPV/DPV Lead Reviewer to complete the PARRF **[RPM]**

Note: If there is a "Safety-related product quality study PMR (see section IV; definition), OBPV/DPV will not complete the PARRF as lead.

c. Generate the PARRF for 506B annual reports. **[Lead Reviewer]**
NOTE: Refer to *JA 860.03: Instructions for Completing the PMR/PMC Annual Report Review Form (PARRF)* for instructions on how to generate and complete the PARRF. (See Appendix A, *Table 3: Primary review discipline and regulatory project management for safety-related study* for additional information.)

i. Procedure for OBPV managed PARRF (when annual report *only* contains Title IX PMRs (Note: this excludes any safety-related product quality PMR) or safety-related PMCs)**:**

a) Consult with the Product Office Lead Reviewer for Title IX PMRs or safety-related PMCs, if the study is off-schedule or at risk of becoming off-schedule. **[OBPV/DPV Lead Reviewer]**

b) Complete the PARRF **[OBPV/DPV Lead Reviewer]**

c) Sign the PARRF **[OBPV/DPV Lead Reviewer, Branch/Lab Chief]**
d) Upload the PARRF through CBER Connect and notify the Product Office PMR/PMC Coordinator. **[OBPV/DPV Lead Reviewer]**
e) Update the statuses of open safety-related PMR/PMCs as needed in the RMS-BLA system **[OBPV/DPV OFFICE PMR/PMC Coordinator]**

ii. Procedure for Product Office managed PARRF (when the Annual Report contains an open PMR/PMC that is not only a safety-related study or a combination of safety-related and a non-safety related study (e.g., PMR under accelerated approval/PREA/animal rule or clinical efficacy PMC):

a) Consult with OBPV for review of Title IX PMRs (Note: this excludes any safety-related product quality PMR) or safety-related 506B PMCs. [Product Office Lead Reviewer]

NOTE: An assigned OBPV/DPV reviewer will complete a separate review memo (uploaded through CBER Connect) and will notify the product office lead reviewer upon upload. **[OBPV/DPV Lead Reviewer**]

b) Complete the PARRF and ensure that the pre-approved "Web Status Explanation" text is used (refer to *R 860.04: Standard Text to use in the PARRF for the Web Status Explanation Field*). Also incorporate any needed OBPV/DPV review memo information regarding safety-related PMRs/PMCs into the PARRF before finalization. **[Product Office Lead Reviewer]**

c) Sign the PARRF. **[Product Office Lead Reviewer, Branch/Lab Chief]**

d) Upload the PARRF through CBER Connect and notify OBPV/DPV Lead Reviewer. **[Product Office Lead Reviewer]**

d. Update the statuses of all open PMRs/PMCs as needed in the PMR/PMC database. **[Office PMR/PMC Coordinator]**

3. 180-Day AA PMR Progress Report (Not part of the Annual Report)

a. Upon submission receipt, complete the review using *T 846.07: 180-DAY AA PMR PROGRESS REPORT REVIEW* ***[Product Office Lead Reviewer]***

b. Sign the review. **[Product Office Lead Reviewer, Branch/Lab Chief]**

c. Upload the review through CBER Connect and notify RPM of review completion. **[Product Office Lead Reviewer]**

d. Notify the Office PMR/PMC Coordinator to update the PMR/PMC database. **[RPM]**

e. Update the PMR/PMC database on the status of the AA PMR(s) using the standardized language from the complete review template. **[Office PMR/PMC Coordinator]**

4. PMR/PMC Submission/Final Study Report

a. **NOTE**: PREA PMRs are not considered fulfilled based on the submission of a Final Study Report (FRS). Either an efficacy supplement to add a new indication or a labeling supplement must be submitted to fulfill PREA PMRs. PREA PMRs will remain in "submitted" status until such a supplement is received and acted upon.

b. If the FSR is a safety-related study under the review purview of OBPV/DPV, contact OBPV/DPV RPM for reviewer assignment. **[RPM]**

> **Note:** The Product Office may have required a safety-related product quality Title IX PMR for unresolved product quality issues related to the risk of a serious adverse drug experience. In this case, the review will occur within the PMR requiring product office and not OBPV. Consult with OBPV/DPV RPM as necessary if unsure.

c. Update the appropriate PMR/PMC in RMS-BLA upon receipt of a Final Study Report (FSR) or a supplement containing a PMR/PMC FSR following the process in the *RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions.* **[Office PMR/PMC Coordinator]**

d. Determine whether the Final Study Report is complete and document the rationale and whether the applicant has fulfilled the commitment in the review memo(s). Discuss issues with the branch chief, division director, applicant and/or other Review Committee Members (OBPV/DPV and other offices), as appropriate. **[Review Committee Member]**

e. Notify the Product Office RPM of inadequate or incomplete Final Study Reports (FSRs). For safety-related PMR/PMC, also notify the OBPV/DPV RPM. **[Review Committee Member]**

f. Issue the "PMC-Final Study Report Not Accepted" letter to the applicant, if appropriate. **[RPM]**

i. For inadequate FSRs missing most of the required information, request that the "PMR/PMC Submission / Final Study Report" be resubmitted in its entirety and notify the Office PMR/PMC Coordinator. **[RPM]**

ii. For incomplete FSRs missing some of the required information, request that the information be provided in an amendment and notify the Office PMR/PMC Coordinator. **[RPM]**

iii. If completing information is submitted before the action due date:

a) Contact RIB to extend the review due date by one (1) year. **[RPM]**

b) Confirm that amendment was received prior to due date then extend the review due date. **[RIB]**

iv. If complete information is not received before the action due date:

a) Document the incomplete information in a review memo, finalize and forward the review memo to the Product Office RPM and Product Office PMR/PMC Coordinator. For safety-related PMR/PMC, under the review purview of OBPV, also notify the OBPV/DPV RPM. **[Review Committee Member]**

b) Close the submission; contact the applicant to resubmit the "PMR/PMC Submission /Final Study Report" in its entirety as a new submission to the BLA. **[RPM]**

c) Contact RIB to return the status of the appropriate PMR/PMC to its previous status or, if the original projected completion date is past, update the status to "delayed." **[Office PMR/PMC Coordinator]**

g. Complete the review of a Final Study Report within the timeframes defined in above in the Policy section (A.5.) and document in the discipline review memo the determination of the PMR/PMC and any missing information not received by the action due date. **[Review Committee Member]**

h. Incorporate any consultant's recommendations into the review memo, finalize the review memo and inform the RPM to initiate final action on the commitment (e.g., issue letter to applicant). **[Review Committee Member]**

NOTE: For any Title IX PMR that is planned to be fulfilled, contact the CBER SWG Executive Secretary of the CBER SWG prior to letter issuance for scheduling/discussion at the CBER SWG **[Office SWG Representative]**.

i. Issue "PMR/PMC-Fulfilled" letter to the applicant; notify the Product Office PMR/PMC Coordinator to update the PMR/PMC database. **[RPM]**

j. Update the PMR/PMC database. **[Office PMR/PMC Coordinator]**

5. Request for Release (Release/Replace) of a PMR:

a. Assess whether the applicant's rationale and/or supporting data are sufficient for evaluating whether the PMR can be either released and/or replaced with a new PMR **[Review Committee Member]**.

i. If additional information is needed from the applicant to evaluate the request, notify the RPM to contact the applicant as soon as possible (no later than 45 days) after receipt of the original release request.

b. For a Title IX, Accelerated Approval, or Animal Rule PMR, contact the CBER SWG Executive Secretary of the CBER SWG for scheduling/discussion at an upcoming CBER SWG (no later than day 45 receipt of the release request). **[Office SWG Representative]**

c. For a PREA PMR, schedule a PeRC presentation by day 45 of receipt of the release request (PREA PMR change) according to the PeRC procedures.

NOTE: see the internal PeRC SharePoint Online site for scheduling and meeting preparation **[Review Committee Member]**

d. Ensure that the final determination on whether to release (or release/release) or communicate a non-agreement to applicant is clearly identified within the discipline review memo. **[Review Committee Member]**

e. Finalize the discipline review memo and notify the RPM to initiate final action (e.g., issue letter to applicant) no later than 60 days after receipt of release request (or within 60 days of receipt of the additional information requested by FDA). [**Review Committee Member]**

f. Draft, obtain concurrence and sign-off, and issue letter to the applicant. Notify the Product Office PMR/PMC Coordinator to update RMS-BLA. **[RPM]**

g. Discuss with senior leadership next steps for receipt of an applicant's request for reconsideration of a non-agreement for PMR release (providing additional information, and/or data) **[RPM]**.

6. Submissions in Response to non-506B PMCs:

a. Assess whether the commitment is still needed or feasible by Applicant; if not document rationale for considering the non-506B PMC as **released** in a discipline review memo. **[Review Committee Member]**

b. Assess if the non-506B PMC is **fulfilled**; document rationale for considering the non-506B PMC as fulfilled in a discipline review memo and incorporate any consultant's recommendations into the discipline review memo. **[Review Committee Member]**

c. Ensure that the final determination of **released** or **fulfilled** is clearly identified within the discipline review memo. Finalize the discipline review memo and notify the RPM to initiate final action on the commitment (e.g., issue letter to applicant). **[Review Committee Member]**

d. Issue the "PMC-Fulfilled" or "PMC-Released" letter to the applicant and notify the Office PMR/PMC Coordinator. **[RPM]**

e. Update RMS-BLA. **[Office PMR/PMC Coordinator]**

7. PMR/PMC Submission: Correspondence Status Update

a. Correspondence Status Update submissions to the application may include:

i. a protocol cross-reference letter,

ii. a request to release an applicant from a PMR/PMC,

iii. the annual status updates for non-506B PMC.

a) **NOTE**: If the milestone schedule change is related to a Title IX PMR or to a PREA PMR see the Scope section for appropriate Job Aids.

b. Ensure that the discipline review memo is complete and notify the RPM of the status determination and action needed. **[Review Committee Member]**

i. **NOTE**: If the request to be released from a PMR is for a FDAAA Title IX PMR, or a safety-related 506B PMC, SWG must provide concurrence. The SWG Office Representative should contact the SWG Executive Secretary to coordinate scheduling/discussion at a future SWG meeting. If the request involves any proposed milestone changes to a PREA PMR, PeRC presentation is required. Contact the Center PREA Liaison and/or refer to *JA*

860.08: Instructions for Processing Applicant Deferral Extension Requests for Pediatric Postmarketing Requirements.

c. Issue a "Release" letter, if appropriate, to release a PMR/PMC. **[RPM]**

i. If appropriate to replace the PMR/PMC with a new PMR/PMC, create and issue the new PMR/PMC following *SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments*. **[Review Committee Members]**

d. Issue a "PMR/PMC Revised Milestone Acknowledgement" letter for Accelerated Approval PMRs and 506B PMCs, or "non-506B PMC Revised Schedule Acknowledgement" letter for non-506B PMC, if appropriate to modify the schedule of Accelerated Approval PMRs or any kind of PMC. **[RPM]**

e. Close the submission and notify the Office PMR/PMC Coordinator. **[RPM]**

f. Update RMS-BLA **[Office PMR/PMC Coordinator]**

D. Data Quality Oversight

1. Check the quality of the data in RMS-BLA and resolve any discrepancies with the RPM/Review Committee Members. **[Office PMR/PMC Coordinator]**

2. Work with the Office PMR/PMC Coordinator to update RMS-BLA to ensure the quality of the data. **[RPM]**

3. Respond to requests concerning discrepancy issues. **[Office PMR/PMC Coordinator]**

4. Issue monthly system discrepancy reports for open PMRs/PMCs to the Office PMR/PMC Coordinators. **[ORO\DIIT\RIB]**

5. Ensure required 506B Annual Reports are submitted on time. If the annual report is late, issue a "PMR/PMC Annual Report Request" letter. **[Office PMR/PMC Coordinator]**

E. Reports

1. Quarterly Postmarket Requirements and Commitments Web page Updates:

a. Run the PMR/PMC Status Report for the Web page at least two weeks before the Web Report is due. Send report to the Center PMR/PMC Liaison for verification. **[ORO\DIIT\RIB]**

b. Coordinate with Office PMR/PMC Coordinators to address any issues identified and ensure all PMRs/PMCs are updated RMS-BLA. **[Center PMR/PMC Liaison]**

c. Review and provide corrected reports to ORO\DIIT\RIB within 10 working days of receipt of report. **[RPM]**

d. Provide the Office of Communication, Outreach, and Development (OCOD) the report to perform a Freedom of Information Act (FOIA) review. **[ORO\DIIT\RIB]**

e. Review the Web Report for privileged and confidential information. Send final report to RIB. **[OCOD]**

f. Send final report containing the required data for posting to CDER's Office of Strategic Programs as directed (usually by the last day of January, April, July, and October) for updating the FDA's Web site. **[RIB]**

2. Federal Register Report:

a. Perform data-lock of all raw data at end of each fiscal year (September 30th). **[RIB]**

b. Organize and analyze reportable PMR/PMC data. **[RIB]**

c. Perform quality review of data to ensure correct reporting status. **[RIB, Center PMR/PMC Liaison]**

d. Send the final data to CDER for inclusion into the final aggregated FDA report. **[RIB, Center PMR/PMC Liaison]**

3. Section 921 (of Title IX of FDAAA) Annual Review of the PMR/PMC Backlog

a. Perform data-lock of all existing backlog data at end of each fiscal year (September 30th). **[RIB**]
NOTE: the "backlog" consists of all PMRs and PMCs that were open (not yet released or fulfilled) as of the date of enactment of FDAAA.

b. Perform quality review of remaining open PMRs/PMCs to ensure correct reporting status. **[Center PMR/PMC Liaison, RIB]**

c. Send the final data to CDER for inclusion into the final FDA report. **[Center PMR/PMC Liaison]**

VIII. Appendices

A. Appendix A: Tables to Support SOPP 8413

1. Table 1: Requirements for the Categories of PMRs/PMCs

2. Table 2: Identification of a PMR/PMC Related Submission to an IND, BLA or NDA

3. Table 3: Primary review discipline and regulatory project management for safety-related study

B. Appendix B: Review Committee Member Considerations for 506B Annual Reports

IX. References

A. References below are CBER internal:

1. Regulatory Job Aids

a. JA 833.03: Instructions for Administratively Closing a Submission in RMS-BLA when a Written Review is not Necessary

b. JA 860.03: Instructions for Completing the PMR/PMC Annual Report Review Form (PARRF)

c. JA 860.04: FDAAA PMR Safety-Related Good Cause Issues

d. JA 860.04.01: Good Cause Data Entry Procedures

e. JA 860.08: Instructions for Processing Applicant Deferral Extension Requests for Pediatric Postmarketing Requirements

2. Regulatory Reference

a. R 860.03: Definitions for PMR/PMC Status Types

b. R 860.04: Standard Text to use in the PARRF for the Web Status Explanation Field

3. RMS-BLA Related Documents

a. RMS-BLA Data Dictionary available in RMS-BLA in the Help menu

b. RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions: available in RMS-BLA under the PMR/PMC information screen by clicking on the "Data Entry Guide" button

c. PMR/PMC Annual Report Review Form (PARRF): available in RMS-BLA under the Communication Templates icon

5. SOPP 8001.5: Inter-Center Consultative Review Process

B. References below can be found on the Internet:

1. Statues and Regulations

a. CFR – Code of Federal Regulations Title 21

b. Federal Food, Drug, and Cosmetic Act (FD&C Act)

c. FDA Modernization Act of 1997 (FDAMA)

d. Food and Drug Administration Amendments Act (FDAAA) of 2007

e. Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012

f. Pediatric Research Equity Act (PREA) of 2007

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

2. Guidance Documents

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

b. 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

3. FDA's Postmarketing Study Requirements and Commitments web page

4. Standard Operating Policies and Procedures

a. SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications to Pending Submissions

b. SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments

X. History

Written/ Revised	Approved By	Approved Date	Version Number	Comment
Laughner	Sonday Kelly, MS, RAC, PMP Director, DROP/ORO	February 15, 2024	14	Updated for PDUFA VII on AA PMR reporting
Monser	N/A	February 27, 2023	13	Technical update for changes due to 2023 CBER reorganization
Laughner	Darlene Martin, MS, PMP ORO/DROP Director (acting)	September 28, 2022	12	Updated for PDUFA VII
Monser	N/A	February 27, 2022	11	Technical update for changes due to 2022 CBER reorganization
Erik Laughner /Meghna Alimchandani	Christopher Joneckis, PhD	July 30, 2021	10	Included definition and administrative handling and review for “safety-related product quality study” Title IX PMR.
Monser	N/A	December 11, 2020	9	Technical Update for retirement of EDR and replacement of “database” with “system”
Erik Laughner / working group	Christopher Joneckis, PhD	August 19, 2020	8	Clarification for review of safety-related PMR/PMC Clarifications of points and processes.

Written/ Revised	Approved By	Approved Date	Version Number	Comment
Menzies/Office PMR/PMC Coordinators	Christopher Joneckis, PhD	April 3, 2017	7	Clarification of points • Role of OBE • Documenting Release/Fulfilled in Discipline Review Memos
Menzies/RMCC Working Group	Christopher Joneckis, PhD	December 19, 2014	6	Updated to move initial data entry from ORO\DIIT\RIB to Office PMR/PMC Coordinators.
O'Leary/ORO\DIIT\RIB	Robert A. Yetter, PhD	August 2, 2010	5	Updated procedures to include findings from BAH study and to implement PMR/PMC Tracking Coordinator role
O'Leary/ORO\DIIT\RIB	Robert A. Yetter, PhD	January 28, 2008	4	Reference and form were updated to reflect database changes
Eastep/ORO\DIIT\RIB	Robert A. Yetter, PhD	April 13, 2007	3	Updated procedures and clarifications of previous version
Eastep/ORO\DIIT\RIB	Robert A. Yetter, PhD	August 21, 2006	2	Revisions to reflect changes in reporting procedures
Eastep/RMCC	Robert A. Yetter, PhD	January 16, 2001	1	Original version

SOPP 8413 Appendix A: Tables to support SOPP 8413

Table 1: Requirements for the Categories of PMRs/PMCs

PMR/PMC Categories	Types	Covered under this SOPP?	Tracked in RMS-BLA	Annual Report required under 601.70 or 314.81?	Reportable by FDA under 506B?
Required Studies/ Clinical Trials (PMRs)	Accelerated Approval (21 CFR 314.510 Subpart H and 601.41 Subpart E)	Yes	Yes	Yes	Yes
PMRs	Deferred Pediatric (21 CFR 314.55(b) and 601.27(b))	Yes	Yes	Yes	Yes
PMRs	Animal Efficacy (21 CFR 314.610(b)(1) and 601.91(b)(1))	Yes	Yes	Yes	Yes
PMRs	FDAAA/Title IX Safety (Section 901)	Yes	Yes	Yes*	Yes
Agreed-upon Studies/ Clinical Trials (506B PMCs)	Clinical Safety, Clinical Efficacy, Clinical Pharmacology, and Non-Clinical Pharmacology (Section 130 FDAMA, 506B of FD&C Act)	Yes	Yes	Yes	Yes
All other Agreed-upon Studies (non-506B PMCs)	CMC and Stability	Yes	Yes	No**	No
Voluntary Studies[#] (Voluntary PMCs)	N/A	No	No	No**	No

* Except when otherwise provided, an applicant may satisfy its obligation to "periodically report" on the status of PMRs and other studies and clinical trials undertaken to investigate a safety issue by submitting the annual reports required under 21 CFR 314.81 or 601.70 if the required elements of information about the status of

the PMR information, set forth in section 505(o)(3)(E)(ii), are accurately and completely provided in that report.

** NDA regulations require that all PMRs/PMCs be reported on in the 314.81 annual report, including non-506B PMCs and Voluntary studies. 601.70 does not require reporting of non-506B studies for biologics. Although Voluntary NDA postmarketing studies are reported on, they are not tracked in CBER's systems.

Non-requested, non-required studies that the applicant has or plans to initiate on its own with generally no expectation that the results will be submitted to FDA.

Table 2: Identification of a PMR/PMC Related Submission to an IND, BLA or NDA

PMR/PMC Type	IND (BIRAMS)	BLA (RMS-BLA)	NDA (RMS-BLA)
PMR/PMC Protocol	Amendment	PMR/PMC Submission/ Correspondence – Status Update (Cross-reference letter)	PMC Submission/Correspondence – Status Update (Cross-reference letter)
PMR/PMC Annual Report (505(o) & 506B only)	Annual Report*	Annual Report/ PMR/PMC Annual Report (may contain 180-Day AA PMR Progress Report)	Annual Report / Changes to an application – PMR/PMC AR (may contain 180-Day AA PMR Progress Report)
Status Update (non-506B)	Not applicable	PMR/PMC Submission/Correspondence - Status Update	PMC Submission/Correspondence – Status Update
180-DAY AA PMR Progress Report	Not appliable	180-Day AA PMR Progress Report	180-Day AA PMR Progress Report
Final Study Report	Not applicable*	Supplement or PMR/PMC Submission/ Final Study Report	Supplement or PMR/PMC Submission/ Final Study Report
Deferral Extension Requested	Not applicable**	PMR/PMC Submission/ Deferral Extension Requested	PMR/PMC Submission/Deferral Extension Requested
Good Cause	Not applicable*	PMR/PMC Submission/ Good Cause	PMR/PMC Submission/Good Cause
All Other PMR/PMC Submissions	Not applicable	PMR/PMC Submission/ Correspondence – Status Update	PMC Submission/Correspondence – Status Update

* PMR/PMC annual reports, Final Study Reports, and submission related to Good Cause must be submitted to the BLA or NDA. They may be submitted to the IND, but if they are, a submission must also be sent to the BLA or NDA referencing the IND submission and all communications must also be submitted to the BLA or NDA.

** If submitted to the IND, contact applicant to submit to BLA/NDA since the review clock and actions are managed in RMS-BLA.

Table 3: Primary review discipline and regulatory project management for safety-related study (a study being conducted specifically to evaluate safety or further investigate a safety issue(s) associated with a product**)**

Submission type	**Assigned primary review discipline**	**Office for regulatory project management and signatory for sponsor letter (if applicable)**
PMR/PMC IND protocol for 506B safety-related study	Pharmacovigilance/Epidemiology (OBPV/DPV)[%] Note: Product Office will review a safety-related product quality study or clinical trial PMR.	Product Office
PMR/PMC annual status report contains only Title IX or 506B safety-related study(ies)* **Excludes product quality studies or clinical trials*	Pharmacovigilance/Epidemiology (OBPV/DPV)	OBPV/DPV (will complete the PARRF and update database as needed)
PMR/PMC annual status report contains Title IX (including product quality studies or clinical trials) and/or 506B safety-related study(ies) AND other Clinical study/trial types	• Clinical (Product Office) completes PARRF • Pharmacovigilance/Epidemiology (OBPV/DPV) completes memo for review of safety-related study with the following study designs: observational epidemiology study, pregnancy registry, study using population-based data sources, survey.	Product Office (will complete the PARRF and update database as needed)
506B safety-related PMC submission to request release/replace or milestone date revision #	Pharmacovigilance/Epidemiology (OBPV/DPV)	Product Office
Title IX PMR submission related to request for release/replace or for good cause justification of missed milestone#	Pharmacovigilance/Epidemiology (OBPV/DPV) unless a “Safety-related Product Quality Study PMR” or clinical trial PMR, which would be reviewed by the Product Office.	Product Office
Final Study Report for Title IX PMR and/or 506B PMC safety-related study	Pharmacovigilance/Epidemiology (OBPV/DPV) Note: Product Office will review a safety-related product quality PMR or clinical trial PMR.	Product Office

If this is safety-related PMR/PMC which has a clinical trial design, it will be reviewed and managed under the Product Office.

% The Clinical (Product Office Reviewer) would contact OBPV/DPV to review the safety protocol.

SOPP 8413 Appendix B: Review Committee Member Considerations for 506B Annual Reports

The following information in the 506B Annual Report should be reviewed:

#	Information	Information submitted in the 506B Annual Report
1.	**Applicant Name**	Applicant's Name as found on FDA Form 356h
2.	**Product Name (trademark and generic, as applicable)**	Product name, and any trademark or /proprietary/generic name(s)
3.	**STN: BLA# or NDA #**	BL ###### or BN######
4.	**Date of original U.S. approval of BLA or NDA:**	Date BLA or NDA was originally approved in the U.S.
5.	**Postmarketing requirement or commitment Number**	Number from the approval letter or other letter establishing a PMR or PMC
6.	**Submission number corresponding to the letter establishing a PMR or PMC**	Submission number resulting in the establishment of the PMR or PMC, example, STN 123456/78
7.	**Date postmarketing study requirement or commitment was issued**	Date of the letter establishing the PMR or PMC
8.	**Description of postmarketing study requirement or commitment**	Description of the PMR or PMC from the letter establishing the PMR or PMC
9.	**Original milestone schedule**	Original milestone schedule from the letter establishing the PMR or PMC, for example • Final study protocol: original date • Patient accrual completion: original date • Study completion: original date • Final study report: original date
10.	**Revised milestone schedule, if appropriate**	Revised milestone schedule, if supplied by the applicant, for example • Final study protocol: updated date • Patient accrual completion: updated date • Study completion: updated date • Final study report: updated date
11.	**Current status of the requirement or commitment**	Current status of PMR or PMC. Status should be: Pending, Ongoing, Delayed, Terminated, or Submitted

#	Information	Information submitted in the 506B Annual Report
12.	**Explanation of Status for the study or clinical trial (This should entail a brief explanation about how the study is progressing in reference to the original projected schedule)**	For each study, does the status explanation include: a. The status of the study and any difficulties encountered in completing the study. b. For each clinical trial, does the status explanation include: 1. The status of the trial 2. Whether enrollment has started 3. Any difficulties encountered in completing the trial 4. The number of participants enrolled to date 5. The expected completion date of the trial 6. Registration information into ClinicalTrails.gov [section 402(j) to the Public Health Services Act (42 USC § 282(j))]