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

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I. Purpose

A. 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 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 PMCs for Premarket Device Applications/Submissions (PMAs/510(k)s) 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.*

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).*

III. Background

A. PMRs/PMCs are generally 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. Congress addressed concerns by FDA and patient/consumer groups about the timely completion of agreed-upon PMC studies by applicants in the FDA Modernization Act of 1997 (FDAMA). Section 130 of FDAMA added section 506B to the Food, Drug and Cosmetic (FD&C) Act.

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 issued guidance for industry in February 2006 to complement the final rule: *FDA 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*. This guidance 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, CBER and the Center for Drug Evaluation and Research (CDER) revised 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.)

4. 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. PMRs and 506B PMCs are reported in the *Federal Register* and on FDA's web site. 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 FDA guidance for industry *FDA 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.*

IV. Definitions

A. 506B Annual Reports – Annual status updates of PMRs or 506B PMC 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, 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; in addition, these commitments are not subject to 506B's reporting requirements.

E. 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.

F. 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.

G. PMR/PMC Annual Report Review Form (PARRF) – Form used by CBER to review the PMR/PMC Annual Reports for 505(o) and 506B reportable PMRs/PMCs.

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 post-approval of a marketing application or a supplement. NOTE: Applicants may be subject to legal penalties 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.

V. Policy

A. CBER will:

1. Track PMR- and PMC-related submissions to ensure closure of the PMR or PMC;

2. Track PMRs, 506B PMCs, and non-506B PMCs in the Regulatory Management System – Biologics License Application (RMS-BLA);

3. Accurately and promptly process PMR- and PMC-related submissions upon receipt;

4. Track and monitor PMR- and PMC-related submissions while under review; **NOTE:** *RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions* is a document that has detailed instructions on entering and updating RMS-BLA.

5. Review PMR- and PMC-related submissions according to the following time-frames:

a. Protocols – CBER will conduct a timely review of all PMR/PMC protocols submitted by the applicant. CBER will provide detailed feedback to the applicant on noted deficiencies and suggested revisions if there are concerns with the submitted protocol design. **Protocols do not have specific review time-frames**.

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** – used for BLA annual reports (21 CFR 601.70) for reportable PMRs/PMCs: **Reviewed on a 3 month time-frame**.

ii. **Changes to an Application/PMC Annual Report (AR)** – used for NDA annual reports (21 CFR 314.81(b)(2)(vii)) including reportable PMRs/PMCs: **Reviewed on a 3 month time-frame**.

c. **Final Reports** – CBER will review a Final 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 PMC, i.e., fulfillment or release.

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

ii. Final Study Report – BLA/NDA Supplement:

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

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

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

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

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

iii. PREA Deferral Extension Requested: **Reviewed on a 45 day time-frame**

6. 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 of the anniversary of U.S. product approvals 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. 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

1. **NOTE:** Labeling changes may not be approved under a PMR/PMC fulfilled letter. All labeling changes, even those requested by FDA, must be submitted as a separate labeling supplement.

D. Milestone schedule for a Title IX PMR is a set of dates used by CBER 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.

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. Submissions to modify the clinical protocol.

2. Submissions made to the BLA or NDA:

a. Once the final protocol has been submitted to the IND, submit the cross-reference notification to the application.

b. 506B Annual Reports are submitted to the BLA (21 CFR 601.70(b)(8)) or to the NDA (21 CFR 314.81(b)(2)(vii)(a)).

c. Milestone schedule changes (e.g., Deferral Extension Requests for PREA PMRs, Good Cause Requests for 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. Supplements containing final study reports or final study reports.

VI. Responsibilities

A. Associate Director for Review Management (ADRM)

1. Ensures that the PMR/PMC tracking and review process steps are implemented consistently and in a timely manner across CBER

2. Supports changes to the PMR/PMC tracking and review process.

3. Ensures that adequate resources are allocated to develop and maintain RMS-BLA with optimal tracking and reporting functionality.

B. CBER's Document Control Center (DCC)

1. Receives and processes all PMR/PMC–related submissions.

2. Logs all PMR/PMC-related submissions into the Document Accountability and Tracking System (DATS).

3. Processes the submission according to usual procedures for that type of submission.

4. Routes the submission to the review division with product responsibility and maintains the record copy files for PMR/PMC-related submissions.

C. Center PMR/PMC Liaison

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

2. Reviews all letters containing PMRs/PMCs prior to issuance of the letters.

D. 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.

   a. Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE) serves as Lead Reviewer if all open PMRs or PMCs were requested by OBE/DE.

   b. The product office serves as Lead reviewer if at least one open PMR/PMC was requested by the product.

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

1. Ensures staff are aware of and adheres 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.

F. Office PMR/PMC Coordinator

1. Responsible for entering, tracking, 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 time-frames (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.

G. Product Office Branch/Lab Chief

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

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

H. Regulatory Project Manager (RPM)

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.

I. Regulatory Information Management Staff (RIMS)

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 Web site.

J. Review Committee Member

1. Conducts a technical, scientific, or clinical review of the submission within the stated review time-frames.

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.

K. Safety Working Group

1. Oversees consistent implementation of procedures associated with Title IX PMRs (such as: good cause or sufficient justification requests) or clinical,

safety related PMCs (requests to release or modify a Title IX PMRs or clinical safety related PMCs).

VII. Procedures

A. Process, Receipt and Route a PMR/PMC-Related Submission

1. Receive and process submissions according to either *SOPP 8110: Submission of* Paper Regulatory Applications to CBER **or** DCC Procedure Guide #22 Procedure for Processing, Routing and Storing Electronic Submissions. [**DCC**]

2. Inform the Office PMR/PMC Coordinator once a submission is determined to contain information associated with a PMR or a PMC. [**RPM**]

   a. **NOTE**: See the "Reviewers" tab under the PMR/PMC in RMS-BLA to identify the responsible review division and the Office PMR/PMC Coordinator.

3. Enter the receipt of the submission into RMS-BLA. [**RPM**]

   a. Ensure all necessary information regarding the PMR/PMC-related submission is accurately and promptly entered into RMS-BLA.

   b. Enter the Office PMR/PMC Coordinator as a member of the Review Committee.

4. Request reviewer assignments from Division Directors or Branch Chiefs, as appropriate. [**RPM**]

   a. NOTE: If the submission pertains to an epidemiologic study (e.g., observational study, registry, or survey), contact the OBE/DE Division Director and OBE/DE-RPM for review assignments

5. Determine Review Committee Members for the submission and inform the RPM [**Division Director, OBE/DE Division Director or OBE/DE-RPM**]

6. Enter Review Committee Members into RMS-BLA and route the submission [**RPM**]

B. Review of submission

7. Notify and route the submission to appropriate Review Committee Members when received. [**RPM**]

8. Ensure that the submission is complete. If the submission is incomplete, inform the RPM indicating the missing information. [**Review Committee Member**]

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

10. Request consult, as needed, with other FDA centers according to *SOPP 8001.5: Intercenter Consultative/ Collaborative Review Process*. [**Review Committee Member**]

11. Perform review within documented review time frames, see Section V.A.5. above, for time frames. For submissions without agreed-upon time frames, coordinate agreed-upon time frame 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))) or to summarize the studies conducted under a PREA PMR. 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.

12. 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**]

C. Finalize the review of the PMR/PMC related submission

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

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

15. Notify and route the amendment to appropriate Review Committee Members when received. [**RPM**]

16. Participate in discussions and decisions to determine final resolution of the submission; such as, consider whether the submission would fulfill a PMR/PMC. [**Branch/ Lab Chief, Office Director/Division Director, CBER SWG for Title IX PMRs**]

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

18. 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 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**

19. 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**]

20. Inform the RPM and Office PMR/PMC Coordinator of completed reviews [**Review Committee Member**]

21. Return the submission to DCC (See *DCC Procedure Guide #8: Procedure For Filing Final Action Packages Containing Paper FDA Correspondence For Marketing Applications - Including Multiple Products* **or** *DCC Procedure Guide #23: Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications*) [**Review Committee Member**]

D. Close the submission

22. Issue PMR/PMC tracking-related correspondence to the applicant in a timely manner using the appropriate Review Letter Templates located on CBER's Intranet Web page. [**RPM**]

23. Forward the complete action package, including the applicant's PMR/PMC related submissions and all CBER reviews, forms and correspondence to DCC following *DCC Procedure Guide #8: Procedure For Filing Final Action Packages Containing Paper FDA Correspondence For Marketing Applications - Including Multiple Products* **or** *DCC Procedure Guide #23: Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications.* [**RPM**]

24. Include the Office PMR/PMC Coordinator, Center PMR/PMC Liaison and the CBER/Regulatory Information Management Staff (RIMS) and consulting offices and divisions that have joint committee responsibility for evaluation of the PMR/PMC-related submissions in the distribution list of key correspondence for the PMR/PMC. [**RPM**]

25. Update RMS-BLA, as appropriate. [**Office PMR/PMC Coordinator**]

26. Perform a quality check to ensure that the appropriate fields within RMS-BLA are populated [**Center PMR/PMC Liaison**]

E. Processing Details for Different Submission Types

1. PMR/PMC Study Protocol

a. Ensure that the cross-reference letter is submitted to the BLA/NDA 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

a. 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.

i. Generate and finalize the PARRF when the 506B Annual Report only contains open Title IX PMRs or safety-related PMCs requested by OBE/DE [**OBE/DE Lead Reviewer**]

a) Sign the PARRF. [**OBE/DE Lead Reviewer, Branch/Lab Chief**]

b) Upload the PARRF into CBER's EDR and notify the Product Office Lead Reviewer. [**OBE/DE Lead Reviewer**]

ii. Generate and finalize the PARRF when the 506B Annual Report contains an open PMR/PMC requested by the product office or when there are open PMRs/PMCs requested by the product office and OBE/DE [**Product Office Lead Reviewer**]

a) Review the status of Title IX PMRs requested by OBE/DE and provide a written review of the required information to complete the PARRF for the Title IX PMR to the Product Office Lead Reviewer [**OBE/DE Lead Reviewer**]

b) Consult with OBE/DE, for safety-related PMCs, if the study is off-schedule or at risk of becoming off-schedule [**Product Office Lead Reviewer**]

c) Incorporate OBE/DE's information onto the PARRF [**Product Office Lead Reviewer**]

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

e) Upload the PARRF into CBER's EDR and notify OBE/DE Lead Reviewer [**Product Office Lead Reviewer**]

b. Ensure that the 506B Annual Report 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 and consider the following: [**Lead Reviewer**]

i. Determine whether the information on the study status and the explanation of status provided by the applicant are appropriate.

ii. Ensure that the study is proceeding in accordance with the *original* schedule.

iii. Summarize the explanation of status provided by the applicant onto the PARRF. The explanation of status is used to update RMS-BLA and may be posted on the FDA Web site.

iv. Ensure that any discrepancies or questions identified during the review are addressed. Provide the RPM with letter ready comments.

c. Notify the RPM if the 506B Annual Report is incomplete or contains updates on non-506B PMCs. [**Review Committee Member**]

d. Request that the applicant submit non-506B PMC status updates for BLAs as a PMR/PMC Submission - Product Correspondence. [**RPM**] **NOTE**: Updates on non-506B PMC should be included in a separate section of the NDA annual report.

e. Issue the "PMC-Incomplete Annual Report Letter" to the applicant if the 506B Annual Report is incomplete and notify the Office PMR/PMC Coordinator. [**RPM**]

i. If the amendment containing the incomplete information is received before the review due date:

a) Contact RIMS to extend the review due date by 90 days. **[RPM]**

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

ii. If the amendment containing the incomplete information is not received before the review due date:

a) Document the incomplete information on the PARRF, finalize and forward the PARRF to the RPM and Office PMR/PMC Coordinator. **[Review Committee Member]**

b) Update the submission type and contact the applicant to resubmit the PMR/PMC – Annual Report in its entirety. **[RPM]**

g. Finalize the PARRF within the time frame identified in Section V.A.5 above, incorporate any consultant's recommendations and notify the RPM and Office PMR/PMC Coordinator when the PARRF is finalized and uploaded into EDR **[Lead Reviewer]**

h. Update RMS-BLA with the status, the explanation of status, and the web status explanation for each PMR and 506B PMC included in the completed PARRF **[Office PMR/PMC Coordinator]**

3. PMR/PMC Submission/Final Study Report

a. **NOTE**: PREA PMRs are not considered fulfilled based on the submission of a Final Study Report. Either an efficacy supplement to add a new indication or a labeling supplement must be submitted to fulfill PREA PMRs.

b. Log-in the submission and determine if PMR/PMC was requested by the Product Office or OBE/DE. If PMR/PMC was requested by OBE/DE route submission to OBE/DE RPM who will manage submission. [**RPM**]
NOTE: If it is unclear as to whether the Product Office or OBE/DE requested the PMR/PMC contact the OBE/DE RPM to determine responsible office.

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 (OBE/DE and other offices), as appropriate. [**Review Committee Member**]

e. Notify the RPM of inadequate or incomplete Final Study Reports (FSRs). [**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 "PMC Submission / Final Study Report" be re-issued 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 RIMS 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. [**RIMS**]

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 RPM and Office PMR/PMC Coordinator. [**Review Committee Member**]

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

c) Contact RIMS 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 V.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**]

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

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

4. Submissions in response to non-506B PMC

a. Assess whether the commitment is still required, needed or feasible; 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**]

5. PMR/PMC Submission: Status Update

a. 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 final determination of the request (**denied**, **granted**, **released**, etc.) is clearly identified within the discipline review memo. Review and finalize a discipline review memo and notify the RPM of the status of the submission [**Review Committee Member**]

i. **NOTE**: If the request to be released from a PMR is for a Title IX PMR, then concurrence must be sought from SWG. Contact the SWG Exec Sec to get on the SWG agenda.

c. Issue a "PMC – 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**]

F. Monitor RMS-BLA

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 database discrepancy reports monthly for existing PMRs/PMCs to the Office PMR/PMC Coordinators. [**RIMS**]

5. Provide PMR/PMC information for the public as mandated (e.g., annual *Federal Register* report, FDA's Web site). [**RIMS**]

6. Conduct an annual review of open PMRs/PMCs. [**Office PMR/PMC Coordinator**]

   a. Review PMR and PMC last annual report receipt date at least quarterly. If the annual report is late, use the "PMC-Annual Report Request" letter template, located on CBER's Intranet Web page, draft the request letter and send to the RPM Branch Chief for approval. Generate a second level STN according to *SOPP 8416: CBER Initiated Second Level STNs*. [**Office PMR/PMC Coordinator**]

   b. Receive draft Annual Report Request letters; coordinate with the Office PMR/PMC Coordinator to finalize the letter. [**RPM Branch Chief**]

   c. Review, approve and serve as signatory authority for the Annual Report Request letters. [**RPM Branch Chief**]

   d. Ensure that RMS-BLA is updated appropriately. [**Office PMR/PMC Coordinator**]

G. Reports

1. FDA Web Page Report:

   a. Draft 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. [**RIMS**]

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

   c. Review and provide corrected reports to RIMS within 10 working days of receipt of report. [**RPM, Office Director**]

   d. Provide the Office of Communication, Outreach, and Development (OCOD) with the Web Report to perform a Freedom of Information Act (FOIA) review. [**RIMS**]

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

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

2. Federal Register Report:

   a. Generate, annually, a CBER summary - PMR/PMC report for the *Federal Register* notice. [**RIMS**]

   b. Send the finalized CBER summary report to the designated FDA unit for drafting the *Federal Register* notice. [**RIMS, Center PMR/PMC Liaison**]

   c. Review the draft *Federal Register* notice and ensure its accuracy with regard to CBER data. [**RIMS, Center PMR/PMC Liaison**]

3. FDAAA Section 921 Mandate:

   a. On an annual basis, reviews the backlog of CBER's PMRs/PMCs and reports to Congress on the activity. [**RIMS, 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

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

IX. References

A. References below are located on CBER's Intranet Web Page (unless otherwise noted):

1. Document Control Center Procedures

   a. DCC Procedure Guide #8: Procedure For Filing Final Action Packages Containing Paper FDA Correspondence For Marketing Applications - Including Multiple Products

   b. DCC Procedure Guide #22 Procedure for Processing, Routing and Storing Electronic Submissions

c. DCC Procedure Guide #23: Procedure for Filing Final Action Packages Containing Electronic FDA Communication for Marketing Applications

2. 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

3. Regulatory Reference

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

4. 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

B. Web links to the references below can be found in the list following the History Section:

1. Statues and Regulations

a. CFR – Code of Federal Regulations Title 21

https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

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

https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/FederalFoodDrugandCosmeticActFDCAct/default.htm

c. FDA Modernization Act of 1997 (FDAMA)

https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/fdama/fulltextoffdamalaw/default.htm

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

https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm

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

http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

f. Pediatric Research Equity Act (PREA) of 2007

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf

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

http://www.fda.gov/OHRMS/DOCKETS/98fr/103000c.htm

2. Guidance Documents

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

b. FDA 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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf

c. Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf

3. Internet Web sites

a. Postmarketing Study Commitments Public Web site

http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

4. Standard Operating Policies and Procedures

a. SOPP 8001.5: Intercenter Consultative/ Collaborative Review Process

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm063119.htm

SOPP 8110: Submission of Paper Regulatory Applications to CBER

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079467.htm

b. SOPP 8401.1: Issuance of and Review of Responses to Information Request Communications and Discipline Review Letters to Pending Submissions

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073078.htm

c. SOPP 8401.7: Action Package for Posting

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm211616.htm

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

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073519.htm

e. SOPP 8416: CBER Initiated Second Level STNs

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073524.htm

X. History

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 RIMS to Office PMR/PMC Coordinators.
O'Leary/RIMS	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/RIMS	Robert A. Yetter, PhD	January 28, 2008	4	Reference and form were updated to reflect database changes
Eastep/RIMS	Robert A. Yetter, PhD	April 13, 2007	3	Updated procedures and clarifications of previous version
Eastep/RIMS	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