

SOPP 8415: Procedures for Developing Postmarketing Requirements and Commitments

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Table of Contents

I.	Purpose	1
II.	Scope	2
III.	Background	2
IV.	Definitions	4
V.	Policy	5
VI.	Responsibilities	9
VII.	Procedures	12
	A. Develop, Review, and Process Title IX, Safety-Related PMRs	12
	B. Develop, Review, and Process Accelerated Approval (AA) or Animal Efficacy Rule (AER) related PMRs	15
	C. Develop, Review, and Process Postmarketing Commitments (506B PMCs or non-506B PMCs)	17
	D. Draft Approval Letter containing PMRs or PMCs	18
	E. Enter New PMRs or PMCs into the Regulatory System	19
VIII.	Appendix	20
IX.	References	20
X.	History	21

I. Purpose

- A.** This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff to define and develop Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs) for drug and biological products.
- B.** The SOPP provides procedures to discuss PMRs/PMCs with the applicant prior to the action goal date; document the rationale/justification for a PMR/PMC; ensure that the PMR/PMC is clearly written and is developed in accordance with Good Review Management Principles and Practices

(GRMP) recommendations.

II. Scope

A. This SOPP covers PMRs and PMCs issued to CBER-regulated human drugs approved with New Drug Applications (NDAs) and Biologics License Applications (BLAs) as well as supplements to a NDA (sNDA) or BLA (BLS). **NOTE:** Abbreviated New Drug Applications (ANDAs) managed in CBER could have a PMR/PMC. General principles of this SOPP would apply in those instances.

B. This SOPP also covers PMCs agreed upon for devices approved under a BLA/BLS that meet the definition of a device under Section 201(h) of the Food, Drug, and Cosmetic (FD&C) Act.

C. This SOPP applies to the development of:

- PMRs related to the Animal Efficacy Rule, accelerated approval, and safety studies or clinical trials required under the Food and Drug Administration Amendments Act (FDAAA);
- PMRs for deferred pediatric studies under the Pediatric Research Equity Act (PREA)
- Agreed-upon, reportable 506B PMCs; and
- Agreed-upon non-506B commitments (i.e., PMC for Chemistry, Manufacturing, and Controls (CMC) and certain product stability studies).

D. This SOPP does not:

- Describe the criteria for determining whether a postmarketing study or clinical trial should be a PMR or a PMC;
- Describe the criteria for determining non-compliance with the conduct of PMRs or the required reporting for PMRs/PMCs;
- Include procedures and responsibilities for PMR/PMC tracking and review (i.e., after a PMR/PMC is issued/agreed upon). Those topics are addressed in SOPP 8413: Postmarketing Requirement/Commitment Related Submissions – Administrative Handling, Review, and CBER Reporting.

III. Background

- A.** In the past, the Food and Drug Administration (FDA) used the term “postmarketing study commitments (PMCs)” to refer to studies or clinical trials conducted by the applicant after FDA approved or licensed a product for marketing. These studies, or clinical trials, were intended to further refine the safety, efficacy or optimal use of a product or to ensure consistency and reliability of product quality. These commitments were either agreed upon by the FDA and the applicant or required by FDA in the following situations:
1. Accelerated approval confirmatory studies (21 CFR 314.510/Subpart H and 601.41/Subpart E), where subsequent studies are required to describe and verify clinical benefit.
 2. Deferred pediatric studies (21 CFR 314.55(b) and 601.27(b)), where studies are required under the Pediatric Research Equity Act (PREA) NOTE: Reference to PREA related PMRs are included to maintain background completeness.
 3. Animal Efficacy Rule, Clinical Efficacy and Safety Studies (21 CFR 314.610(b)(1)/Subpart I and 601.91(b)(1)/Subpart H) where studies to demonstrate safety and efficacy in humans are required at the time of use.
- B.** Section 130(a) of Title I of the Food and Drug Administration Modernization Act of 1997 (FDAMA) added a provision (section 506B) to the FD&C Act which mandates applicants to report annually on the status of PMRs and reportable PMCs, and obligated FDA to make certain information about these PMRs/PMCs is publicly available.
- C.** In 2007, Section 901, in Title IX of FDAAA created section 505(o) of the FD&C Act which authorized FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of new safety information.
1. FDAAA states that studies and clinical trials may be required for one of three purposes:
 - a. To assess a known serious risk related to the use of the drug,
 - b. To assess signals of serious risk related to the use of the drug, or
 - c. To identify an unexpected serious risk when available data indicate the potential for a serious risk.
 2. In order to require a clinical trial or study, FDA must first make a determination that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk. Furthermore, FDA must make a determination

that the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) is not sufficient to assess this serious risk.

NOTE: The pharmacovigilance system under section 505(k)(3) will be referred to as “CBER Sentinel.”

3. Section 901 of FDAAA requires applicants to submit a milestone schedule for completion of each study/clinical trial and to report periodically on the status of any study or clinical trial required.
 4. Circumstances may arise where unresolved product quality issues can be related to the risk of a serious adverse drug experience and therefore may qualify as a safety-related product quality study PMR as opposed to a non-506B PMC. See the *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry (2019)* for safety-related examples.
- D. The 2022 Food and Drug Omnibus Reform Act (FDORA) allows, but does not mandate, the FDA to require that confirmatory accelerated approval studies/trials already be underway prior to accelerated approval or within a specified time from the date of approval. FDORA also requires applicants after approval to report on accelerated approval postapproval study progress every 180 days to ensure these studies are being done with due diligence until the final study report has been submitted to FDA.

IV. Definitions

- A. 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, in writing, to conduct; 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).
- B. 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.
- C. Non-506B, Non-Reportable, Postmarketing Commitments (non-506B PMC) –** Any Chemistry, Manufacturing, and Controls (CMC) study, agreed, in writing, to be conducted, 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.
- D. PMR/PMC Schedule Milestones –** The specific study dates for completing

activities related to conducting a PMR/PMC.

- E. 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.
- F. 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.
- G. CBER Sentinel Sufficiency Assessment** – Under section 901 of FDAAA, a required determination by CBER of the sufficiency (i.e. capability) of CBER Sentinel to further characterize serious risk(s) of concern. Sentinel insufficiency serves as a justification for whether a Title IX PMR is warranted.
- H. 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.
- I. Voluntary Postmarketing Study or Trial** – A study or clinical trial conducted on an applicant’s own initiative without a formal request by FDA (i.e., not in an FDA letter).
- J. “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.
- K. “Safety-related Product Quality Study”** (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.

V. Policy

A. CBER will:

1. Use the CBER Safety Work Group (SWG) for review and feedback of all proposed PMRs invoking Title IX authorities and any proposed safety related 506B PMCs.

2. Develop and communicate to applicants all PMRs/PMCs using a standardized process.
3. Meet the targeted date for communication of any proposed PMCs as specified in the filing letter
4. Meet the targeted communication date for any proposed PMR as specified in the filing letter:
 - a. For standard new molecular entity (NME) NDAs and original BLAs, CBER will communicate details on anticipated PMRs no later than 8 weeks before the PDUFA action goal date.
 - b. For priority NME NDAs and original BLAs, CBER will communicate details on anticipated PMRs no later than 6 weeks before the PDUFA action goal date.
 - c. CBER will use *T 910.04: [8-] OR [6-] Week Postmarketing Requirement (PMR) [and Postmarketing Commitments (PMCs)] Communication* to communicate the list of proposed PMRs (and PMCs if ready).

Note: An anticipated PMR is a PMR required as a condition of approval based upon information **provided in the original application at the time of submission** and not as a result of a subsequent information request and/or an amendment. The pre-specified communication target date will not apply for unanticipated PMRs.

5. Document discussions and agreements with the applicant relating to PMRs/PMCs in CBER's Regulatory Management System as per the appropriate CBER SOPPs (see IX. References at end of this SOPP).

Note: FDAAA gives FDA the authority to require PMRs without prior agreement from the applicant. Generally, CBER will work with the applicant on the design of a PMR study and to come to agreement on feasible milestones for completing the study. For PMCs, the applicant should submit a written agreement to conduct the PMCs.

6. Review the rationale for a PMC.
 - a. A PMC must be agreed upon, in writing, between FDA and the applicant.
 - b. A PMC will be requested only if the objectives are important to further the knowledge of the safe and effective use of the product.

7. Review PMR/PMC descriptions within the Office/Division to ensure that they are clearly written and contain the appropriate milestone schedule. The milestone schedule should include a final due date for the data that would result in a submission that addresses the issue for the stated PMR/PMC. Milestones include the final protocol submission date, the study completion date, and the final report submission date. **NOTE:** Additional interim milestones may be added to a PMR/PMC if necessary to provide enhanced oversight. For example, a pre-specified interim analysis report date.
8. Collaborate with the applicant to develop the milestone schedule for the PMR/PMC. FDAAA gives FDA the authority to require PMRs without prior agreement from the applicant.
9. Include a clear and concise justification for the determination of the need for any PMR/PMC, as well as whether the study/clinical trial will be 506B reportable or not. **NOTE:** Justification for Title IX-related PMRs will include reason(s) why CBER Sentinel is insufficient to further characterize serious risk(s) of concern.
10. Strive to resolve all potential non-506B PMC issues during the review cycle and minimize the generation of non-506B PMC.
11. Request status updates on non-506B PMC for BLA/BLS as “Postmarketing Study Commitments – Status Update” and for NDA/sNDA within a separate section of the NDA annual report (21 CFR 314.81(b)(2)(viii)).
12. Require the applicant to report periodically on the status of any study or clinical trial required under Section 505(o)(3)(E)(ii). In addition, require an applicant to report annually on the status of any PMC or PMR studies of clinical trials as per section 506B of the FDCA and 21 CFR 601.70.
13. Ensure that all PMRs and PMCs in any approval letter are entered into the appropriate PMR/PMC tracking database within one business week.

B. CBER will not:

1. Include in the approval letter or otherwise record or track voluntary studies or trials.
2. Request a PMC for a study/clinical trial that is covered by other regulations (e.g., safety data updates or adverse event reports under 21 CFR 600.80).
3. Require a Title IX PMR for a study/clinical trial that is covered by other

regulations (e.g., periodic safety reports or adverse event reports under 21 CFR 600.80 or studies in CBER Sentinel when CBER Sentinel is sufficient to further characterize the serious risk(s) of concern).

C. Types of 506B PMC studies include:

1. **Clinical Efficacy** – Human studies intended to further characterize the effectiveness or optimal use of a product.
2. **Clinical Pharmacology** – Human studies to further determine the effects of the product on the body, including pharmacokinetics (what happens to the product while in the body), pharmacodynamics (the effects of the product, as pertaining to a subject's biochemistry and physiology), toxicity, and drug interaction.
3. **Clinical Safety** – Human studies intended to gather additional information on the safety of a product, e.g., at different dosage levels. These include immunogenicity studies intended to further define an immune response elicited by the introduction of an antigen (e.g., protein.)
4. **Non-Clinical Toxicology** – Non-human studies (e.g., animal studies, in vivo animal models) to further characterize carcinogenicity, teratogenicity, reproductive toxicology, biopharmaceutic and pharmacokinetic properties of a product.

D. Additional information concerning non-506B PMC:

1. CMC studies may include manufacturing, stability, and other studies that do not have a direct safety endpoint
2. Non-506B PMC studies are not subject to 506B reporting requirements described under 21 CFR 601.70 for BLAs. For NDAs, 21 CFR 314.81(b)(2)(viii) requires an applicant to advise the FDA on the status of non-506B PMCs in a separate section of the NDA annual report.

E. Additional information concerning voluntary studies:

1. Voluntary studies or clinical trials are not required or agreed upon.
2. Voluntary studies or clinical trials are not subject to 506B reporting requirements. Although for NDAs, 21 CFR 314.81(b)(2)(viii) requires the applicant advise the FDA on the status of voluntary studies or clinical trials in a separate section of the NDA annual report.
 - a. There are no provisions to modify the original milestone dates as stipulated under 21 CFR 314.81(b)(2)(vii)(a)(8) and 21 CFR

601.70(b)(8). A revised schedule can be submitted along with reasons for the revision; however, FDA will use the original study schedule to determine the study progress.

- b. The following milestone dates should be included in the schedule and in the approval letter or alternative correspondence (e.g., PMC Study Schedule Notification letter) when the PMR/PMC is required or agreed upon. These dates should be captured and updated as necessary in RMS-BLA, and may include:
- Final protocol submission date.
 - Study/clinical trial completion date or a date in relation to another milestone listed above (e.g., X months after final protocol submission).
 - Final report submission date or time related to the actual completion date (e.g., within X months after study completion).

VI. Responsibilities

A. Branch/Lab Chief

1. Participates in discussion and provides input on the PMR/PMC;
2. Ensures that a clear and concise justification for requiring or recommending a PMR/PMC is clearly described in the discipline review memo;
3. Notifies the CBER Sentinel Team of serious risk(s) that may need to be further characterized in a safety postmarketing requirement study. NOTE: This refers to the pharmacovigilance discipline Branch Chief, in the Division of Pharmacovigilance/OBPV;
4. Ensures that the PMR/PMC description clearly communicates the objectives of the PMR/PMC in order for the applicant to adequately address the PMR/PMC; and
5. Ensures that the Review Committee Members resolve differences with the applicant.
6. Ensures that the final milestone schedule is both feasible and reasonable; and provides concurrence on the PMRs/PMCs.

B. CBER Sentinel Team

1. Determines the sufficiency of CBER Sentinel to further characterize the serious risk(s) of concern under section 901 of FDAAA and
2. Participates in the SWG meeting.

C. CBER Safety Working Group (SWG) Office Representative

1. Serves as the point of contact between the Review Committee Members and the CBER SWG Executive Secretary, and
2. Participates in the SWG meeting.

D. CBER SWG Executive Secretary

1. Schedules CBER SWG meeting, and
2. Invites appropriate participants to the meeting.

E. 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 before issuance of the letters; and
3. Participates in the SWG meeting.

F. Division Director

1. Participates in discussion and provides input on the PMR/PMC;
2. Ensures that staff are aware of and adhere to established policies regarding PMR/PMC development;
3. Ensures that the discipline memo for pharmacovigilance includes the justification for Title IX-related PMRs and the reason(s) why CBER Sentinel is insufficient to further characterize the serious risk(s) of concern (OBPV/DPV Division Director);
4. Ensures that all PMRs/PMCs are applied consistently across the Office/Division and meets the general policy guidelines in this SOPP;
5. Ensures that adequate resources are committed to review, track, and close each PMR or PMC;

6. Receives periodic updates on PMR/PMC status within the division; and
7. Provides concurrence on all PMRs/PMCs before issuing the action letter.

G. Office Director

1. Reviews potential Title IX-related PMRs and ensures that the PMR justification includes reason(s) why CBER Sentinel is insufficient to further characterize serious risk(s) of concern prior to CBER SWG meeting; and
2. Receives concurred PMRs before the final regulatory decision.

H. Office PMR/PMC Coordinator

1. Reviews PMR/PMC for clarity and study milestones (**NOTE:** when reviewing proposed milestones, it is recommended to use the last day of a month as the due date. (i.e. May 31, XXXX));
2. Enters PMR/PMC into the tracking system; and
3. Uses the RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions for detailed instructions on entering and updating RMS-BLA.

I. PMR/PMC Lead

1. Serves as the technical lead in the development, negotiation, and documentation of a PMR or PMC; and
2. Participates in contacting the applicant after determining the need for a PMR or PMC.

J. Regulatory Project Manager (RPM)/Chair

1. Serves as the point of contact and communicates with appropriate personnel, sends the draft PMRs/PMCs to the applicant;
2. Ensures that each PMR/PMC is drafted and numbered sequentially in the approval letter;
3. Checks to ensure that RMS-BLA is populated post-approval with the PMRs/PMCs, including the study schedule milestones;
4. Coordinates review-specific communications (e.g., protocol review comments from the review committee members) with the applicant for PMR/PMC content-related issues pre- and post-approval; and

5. Uses the RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions for detailed instructions on entering and updating PMRs/PMCs in CBER's regulatory system.

K. Review Committee Members

1. Identifies potential PMR/PMC issues, participates in discussions and provides input on the development of the PMR/PMC [**NOTE:** when developing milestones, it is recommended to use the last day of a month as the due date. (i.e. May 31, XXXX)].
2. The OBPV/DPV Branch Chief notifies the CBER Sentinel Team of serious risk(s) that may need to be further characterized in a postmarketing requirement study, and includes the CBER Sentinel Team in review team discussions. The CBER Sentinel Team reviews the sufficiency of CBER Sentinel to assess the serious risk(s). Review team concurrently discusses potential safety PMR study design.
3. Fully describes a clear and concise justification in the discipline review memo for why each PMR/PMC is needed.
4. The justification for any needed Title IX-related PMRs will include reason(s) why CBER Sentinel is insufficient to further characterize serious risk(s) of concern.
5. Drafts the PMR/PMC description to clearly communicate the objectives of the PMR/PMC for the applicant to address.
6. Circulates the PMR/PMC description to the Branch/Lab Chief(s) for concurrence prior to communication to the applicant by the RPM.
7. Reviews and participates in resolving any differences between the objectives and study schedule milestones after the draft PMR/PMC descriptions have been circulated.

L. SWG Co-Chairs

1. Lead the CBER SWG meetings.

VII. Procedures

A. Develop, Review, and Process Title IX, Safety-Related PMRs

1. Identify potential PMR review issue(s). [**Review Committee Members**]

NOTE: The identification of potential Title IX, safety related PMRs (including “Safety-related Product Quality Study” PMR) and involvement with the CBER Sentinel Team should occur during the initial review of the submission; presentation to SWG should occur no later than 10 weeks (standard review) or 8 weeks (priority review) before the action goal date.

2. Participate in discussions and provide input on potential PMR review issues at a pharmacovigilance planning meeting. **[Review Committee Members, Branch/Lab Chief, Product Division Director, OBPV/DPV Division Director, CBER Sentinel Team]** **NOTE:** These discussions could occur during review committee meetings, at office specific OBPV/DPV-Division Level Safety Assessment Meeting (SAM) or other meetings as appropriate.
3. Draft the CBER Sentinel Sufficiency Assessment memo if a potential Title IX PMR is warranted. **[CBER Sentinel Team/OBPV].**
4. Participate in the review of draft PMR descriptions and milestone schedules for clarity, feasibility and consistency with similar PMRs. **[RPM, Chair, Office PMR/PMC Coordinator, Review Committee Members, Branch/Lab Chief, Division Director]**
5. Include the rationale for the PMR in the discipline review memo(s). **[Review Committee Members]**
6. Notify Office Safety Working Group (SWG) Representative of potential PMRs. **[RPM/Chair]**
7. Informally notify SWG Exec Sec of potential Title IX PMRs. **[SWG Office Reps]**
8. Provide the PMR concept, which may include a projected milestone schedule, to supervisors for review and agreement. **[Review Committee Members]**
9. Provide concurrence on PMR concept. **[Branch/Lab Chief, Division Director]**
10. Provide concurred PMR concept to Office Director, Division Director, CBER Office SWG Representative. **[RPM/Chair]** **NOTE:** Obtain CBER SWG concurrence on the PMR concept before notifying the applicant. Review PMR concept prior to CBER SWG meeting. **[Division Director, OBPV and Product Office Directors]**
11. Provide Review Committee Member names that should be invited to the CBER SWG to CBER Office CBER SWG Representative. **[RPM, Chair]**

12. Receive PMR concept and Review Committee Member's names. Forward the information to the CBER SWG Executive Secretary. **[CBER SWG Office Representative]**
13. Place PMR concept on an upcoming CBER SWG meeting agenda and invite Review Committee Members to CBER SWG. **[CBER SWG Executive Secretary]**
14. Conduct the CBER SWG meeting. **[CBER SWG Co-Chairs]**
 - a. Attendees should include, as appropriate:
 - i. RPM,
 - ii. Chair,
 - iii. Review Committee Members,
 - iv. Branch/Lab Chief,
 - v. Division Director,
 - vi. CBER SWG Office Representative,
 - vii. CBER SWG Executive Secretary,
 - viii. SWG Co-Chairs,
 - ix. Office PMR/PMC Coordinator
 - x. CBER Sentinel Team
15. Provide a presentation or handouts summarizing key points of each Title IX PMR. **[Review Committee Members]** **NOTE:** To ensure that SWG has the full understanding of the PMR, include summaries of any other potential PMR and reportable PMC anticipated to be included in the approval of the application or supplement.
16. Contact applicant, after CBER SWG meeting, to initiate PMR negotiations. For original and priority review applications, CBER must communicate the list of ALL anticipated PMRs (Title IX, PREA, Accelerated Approval, Animal Rule) by the target communication date as specified in the filing letter using *T 910.04: [8-] OR [6-] Week Postmarketing Requirement (PMR) [and Postmarketing Commitments (PMCs)] Communication*. **[Lead, RPM, Chair]**
17. Serve as Lead to negotiate study design and milestone schedules for Title IX Epidemiological Observational PMR studies. **[OBPV DPV Committee Member]**
18. Serve as Lead to negotiate a "Safety-related Product Quality Study"(under Title IX) and related milestone schedules. **[Product Office CMC Review Committee Member]**

19. Complete and finalize the CBER Sentinel Sufficiency Assessment memo four weeks before the action due date for priority reviews and eight weeks before the action due date for standard reviews. **[CBER Sentinel Team/OBPV]**

20. Participate in discussions about content and schedule milestones for draft PMRs. Obtain general agreement on PMR studies and request written agreement from applicant on the study design, milestones, and other details of the PMRs. **[Lead, RPM/Chair]**

Note: If applicant proposed has requested subparts of a PMR with sets of milestones, this is difficult to track and should be disallowed.

21. Receive written agreement from the applicant as an amendment to the file and send the amendment to the Review Committee for review. **[RPM/Chair]**

Note: While agreement with the applicant is ideal, CBER may require the language and milestones as initially proposed.

22. Review the amendment to ensure that it is accurate and complete. If the amendment is not accurate and complete, contact the applicant to correct the amendment. **[Lead, RPM/Chair]**

23. Prepare draft approval letter containing PMRs. **[RPM/Chair]**

B. Develop, Review, and Process Accelerated Approval (AA) or Animal Efficacy Rule (AER) related PMRs

1. Identify studies not included in the AA or AER applications and begin to discuss appropriate PMR studies or clinical trials. **[Review Committee Members]**

2. Participate in discussions and provide input on anticipated AA or AER PMR studies. **[Review Committee Members, Branch/Lab Chief]**

3. Notify management of anticipated AA or AER PMRs. **[RPM, Chair]**

4. Prepare discipline review memos including technical rationale of the AA or AER PMRs and forward to RPM and Chair. **[Review Committee Members]**

5. Provide concurrence on discipline review memos. **[Branch/Lab Chief, Division Director]**

6. Provide concurred AA or AER PMRs to Office Director, Division Director,

Office PMR/PMC Coordinator and the Center PMR/PMC Liaison. **[RPM, Chair]**

7. Receive concurred AA or AER PMRs prior to final regulatory decision. **[Division Director, Product Office Director, Office PMR/PMC Coordinator, Center PMR/PMC Liaison]**
8. Contact applicant, after internal meetings, to initiate AA or AER PMR negotiations. For original and priority review applications, CBER must communicate the list of ALL anticipated PMRs (Title IX, PREA, Accelerated Approval, Animal Rule) by the target communication date as specified in the filing letter using *T 910.04: [8-] OR [6-] Week Postmarketing Requirement (PMR) [and Postmarketing Commitments (PMCs)] Communication*. **[RPM/Chair]**
9. Participate in discussions about content and schedule milestones for draft AA or AER PMRs. Obtain general agreement on AA or AER PMR studies and request written agreement from applicant. **[Lead, RPM/Chair, Branch/Lab Chief, Division Director]**
 - a. Serve as lead to negotiate study/clinical trial design and details, and milestone schedules for all AA or AER PMR studies **[Product Office Clinical Review Committee Member]**
10. Receive written agreement from the applicant as an amendment to the file and send the amendment to the Review Committee for review. **[RPM/Chair]**
11. Review the amendment to ensure that it is accurate and complete. If not accurate and complete, contact the applicant to correct the amendment. **[Lead, RPM/Chair]**
12. Prepare draft approval letter containing the PMR(s). **[RPM/Chair]**

C. Develop Review, and Process PREA PMRs

1. Confirm the application contains all deferred pediatric studies (PREA PMRs) as agreed upon in the IND (agreed iPSP) are in the application. **[RPM, Chair]**
2. Schedule a Pediatric Review Committee (PeRC) or Oncology subcommittee of PeRC meeting according to the timelines outlined in the PeRC scheduling procedure. **[RPM]**
3. Attend and present at the PeRC. **[Clinical Reviewer]**

4. Contact applicant (after PeRC) if there changes to the deferred studies/milestones. **[Lead, RPM/Chair]**

Note: Even if there are no changes to the originally planned deferred studies/milestones (see Policy A. 4. above) for original and priority review applications, CBER must still communicate the list of ALL anticipated PMRs (Title IX, PREA, Accelerated Approval, Animal Rule) by the target communication date as specified in the filing letter using *T 910.04: [8-] OR [6-] Week Postmarketing Requirement (PMR) [and Postmarketing Commitments (PMCs)] Communication*.

5. Ensure the clinical review memo as well as the SBRA provides appropriate rationale for all PREA PMRs. **[Clinical Reviewer]**
6. Prepare draft approval letter containing the PMR(s). **[RPM/Chair]**

D. Develop, Review, and Process Postmarketing Commitments (506B PMCs or non-506B PMCs)

1. Identify potential review issues. **[Review Committee Member]**
2. Participate in discussions and provide input on potential PMC review issues. **[Review Committee Member, RPM/Chair, Branch/Lab Chief]**

NOTE: The PMC objectives should include the following:

- a. What does CBER want the applicant to do?
 - b. What type of information or data is needed to fulfill the PMC? For example, the type of study results or information CBER expects.
 - c. When does CBER want the study results or report? **NOTE:** If an exact date cannot be determined, then include an estimated date.
 - d. Refer to [Appendix A](#) (Development of Non-506B Postmarketing Commitments (PMC) – Questions and Answers and Regulatory Reference *R 910.01: Development of Non-506B PMC*) for additional information on how to develop and write non-506B PMCs.
3. Review PMCs for clarity, feasibility, and consistency with other similar PMCs. **[Review Committee Member, RPM/Chair, Branch/Lab Chief, Office PMR/PMC Coordinator, Center PMR/PMC Liaison as needed]**
 4. Determine if potential review issues should be made an inspectional recommendation or a non-506B PMC. See *R 910.01: Development of Non- 506B PMC* for additional information. **[Review Committee Member]**

5. Include the scientific and regulatory rationale for the PMC in the discipline review memo. **[Review Committee Member]**
 - a. **NOTE:** any proposed safety related PMCs should be briefly discussed at a SWG meeting.
6. Contact the applicant, after internal discussions, to initiate PMC discussions. **[RPM/Chair]**
7. Participate in discussions about what needs to be studied, what data or information are expected to fulfill the commitment, and a fulfillment date for each PMC. Obtain general agreement on PMC studies and request written agreement from the applicant. **[RPM/Chair]** **NOTE:** A fulfillment date should be listed for each PMC [use the last day of a month as the due date. (i.e. May 31, XXXX)], even if the date is estimated.
8. Review the amendment to ensure that it is accurate and complete. If not accurate and complete, contact the applicant to correct the amendment. **[RPM/Chair]**
9. Prepare draft approval letter containing PMCs. **[RPM/Chair]**

E. Draft Approval Letter containing PMRs or PMCs

1. Draft the approval letter using the appropriate letter template. Please refer to CBER's Letter Templates for the most recent approved template. Ensure that the agreed upon PMR/PMC is represented in the letter as submitted by the applicant. **[RPM/Chair]**
2. Ensure that each PMR/PMC included in the letter is numbered sequentially. **[RPM/Chair]**
3. Provide the "mature" draft approval letter to the Office PMR/PMC Coordinator, the CBER SWG Executive Secretary (for Title IX-related PMRs and clinical, safety-related PMCs), and the CBER PMR/PMC Liaison. **[RPM/Chair]**
4. Review the PMRs and PMCs and accompanying letter language for accuracy. **[Office PMR/PMC Coordinator]**
5. Forward the "mature" draft approval letter that contains the type of PMR/PMC listed below to the indicated person: **[CBER SWG Executive Secretary]** for Title IX-related PMRs and clinical, safety-related PMCs and **Center PMR/PMC Liaison** for all other approval letters containing PMRs/PMCs] **NOTE:** A letter may need to be reviewed by more than one

person, depending on the types of PMRs/PMCs it contains.

- a. Review Title IX-related PMRs and clinical, safety related PMCs and provide feedback to the CBER SWG Executive Secretary. **[CBER SWG Co-Chairs]**
 - b. Review PREA PMRs and provide feedback to the Center PMR/PMC Liaison. **[Senior Advisor for Pediatric Regulatory Review]**
 - c. Review Accelerated Approval PMRs and provide feedback to the Center PMR/PMC Liaison. **[ADRM or designee]**
 - d. Review AER PMRs and provide feedback to the Center PMR/PMC Liaison. **[Senior Advisor for Counterterrorism/Medical Countermeasures or designee]**
 - e. Review device related non-506B PMCs and provide feedback to the Center PMR/PMC Liaison. **[Senior Advisor for Devices]**
 - f. Review all other types of PMC. **[Center PMR/PMC Liaison]**
6. Ensure that the individuals designated above review the “mature” draft approval letter and provide any collected feedback to the RPM/Chair. **[CBER SWG Executive Secretary** for Title IX-related PMRs and clinical, safety- related PMCs and **Center PMR/PMC Liaison]**
 7. Edit, finalize, and issue the approval letter. **[RPM/Chair, Review Committee Members, Branch/Lab Chief, Office PMR/PMC Coordinator]**

F. Enter New PMRs or PMCs into the Regulatory System

1. Ensure the approval letter or other notification letter establishing a PMR or PMC is entered in CBER’s regulatory system and uploaded into CBER’s Electronic Repository (CER) and notify the Office PMR/PMC Coordinator. **[RPM]**
2. Enter all PMRs/PMCs from the approval letter within one business week into CBER’s regulatory system following the instructions found in the RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions document. **[Office PMR/PMC Coordinator]** **NOTE:** The Office responsible for approving the submission is responsible for entering all PMRs and PMCs included in the approval or notification letter into the regulatory system.
3. Perform a quality check to ensure that the appropriate fields within

CBER's regulatory system are populated with the PMRs and PMCs from the approval or notification letter. **[Center PMR/PMC Liaison]**

VIII. [Appendix](#)

- A. Development of Non-506B Postmarketing Commitments (PMC) – Questions and Answers

IX. References

- A. References below are CBER internal:

1. RMS-BLA Data Entry for Postmarketing Requirements/Commitments and Related Submissions, located within RMS-BLA
2. R 910.01: Development of Non-506B PMC
3. T 910.04: [8-] OR [6-] Week Postmarketing Requirement (PMR) [and Postmarketing Commitments (PMCs)] Communication

- B. References below can be found on the Internet:

1. [Food and Drug Administration Amendments Act \(FDAAA\) of 2007](#)
2. [Food and Drug Administration Modernization Act \(FDAMA\) of 1997](#)
3. [CFR – Code of Federal Regulations Title 21](#)
4. [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](#)
5. [FDA Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act](#)
6. [Guidance for Review Staff and Industry: Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications](#)
7. [Postmarketing Study Commitments Public Web site](#)
8. [SOPP 8413: Postmarketing Requirement/Commitment Related Submissions – Administrative Handling, Review, and CBER Reporting](#)
9. [SOPP 8401: Administrative Processing of Original Biologics License](#)

[Applications \(BLA\) and New Drug Applications \(NDA\)](#)[10. SOPP 8401.2: Administrative Processing of BLA and NDA Supplements](#)**X. History**

Written/ Revised	Approved By	Approved Date	Version Number	Comment
Erik Laughner	Sondy Kelly, MS, RAC, PMP Director, DROP/ORO	February 15, 2024	9	FDORA updates and adding PMR/PMC communication template
Erik Laughner	Darlene Martin, MS, PMP ORO/DROP Director (acting)	September 28, 2022	8	Updated for PDUFA VII
Monser	N/A	February 27, 2022	7	Technical update for changes related to 2022 CBER reorganization.
Erik Laughner/Meghna Alimchandani	Christopher Joneckis, PhD	September 3, 2021	6	Updated to include safety-related product quality studies as Title IX PMRs.
Monser	N/A	December 11, 2020	5	Technical Update for retirement of the EDR and replacement with CER and to replace "database" with "system"
Erik Laughner/Meghna Alimchandani	Christopher Joneckis, PhD	August 26, 2019	4	Updated to include revised process for Title IX- PMR development using the CBER Sentinel Team
Menzies/Office PMR/PMC Coordinators	Christopher Joneckis, PhD	April 3, 2017	3	Added the role of Center PMR/PMC Liaison,
Menzies/RMCC Working Group	Christopher Joneckis, PhD	December 19, 2014	2	Updated to include revised procedures
Eastep/RIMS	Robert A. Yetter, PhD	Sept 12, 2008	1	Original version

SOPP 8415 Appendix A: Development of Non-506B Postmarketing Commitments (PMC) – Questions and Answers

Non-Reportable Postmarketing Commitments (non-506B PMC) are also known as Postmarketing Study Commitments. A non-506B PMC is any study to assess drug or biologic product quality that is not required for approval; yet, the review committee deems necessary to provide complete quality information. A non-506B PMC is agreed upon, in writing, by the applicant and FDA. Studies may include:

- **Stability** – Submission of additional stability data that support the approved expiration date of the product or further supports the characterization of the product's stability; or
- **Chemistry, Manufacturing, and Controls (CMC)** – Completion of studies and submission of associated data related to equipment qualification, process validation, product quality, and procedures.

The intent of non-506B PMCs is to obtain product and manufacturing related data not available during the application or supplement review cycle, to obtain data that provides additional assurance that manufacturing practices are adequate, to perform a study that is only feasible to conduct post-approval or to further analyze a product or manufacturing process. These studies are not subject to 506B PMC reporting requirements, although New Drug Application (NDA) regulations require under 21 CFR 314.81(b)(2)(viii) that an applicant advise the FDA on the status of each of these types of non-506B PMCs in a separate section of their annual report.

Questions:

Q1. What is a non-506B PMC?

A1. A Non-Reportable Postmarketing Commitment (non-506B PMC) is any study to assess drug or biologic product quality that is not required for approval; yet, the review committee deems necessary to provide complete quality information. A non-506B PMC is concurred, in writing, by the applicant and FDA. Studies may include manufacturing, stability, and other studies that do not have primary safety as an endpoint.

Q2. What should you consider when developing a non-506B PMC?

A2. There are a number of issues to consider:

1. Is the generation of the non-506B PMC based on a risk/benefit model? If the incomplete information is critical to “approving” an application or supplement and cannot be obtained and reviewed within the review cycle, the review committee should not approve the application or supplement but should, instead issue a Complete Response (CR) letter.

2. Are the scientific and regulatory rationales for agreeing-upon the non-506B PMC included in the review memo (and SBRA)? **NOTE:** Do not include the scientific and regulatory rationales in the non-506B PMC.
3. Have you discussed and obtained concurrence for the non-506B PMC with management before speaking with the applicant?
4. Is the request necessary and does the request provide regulatory information?
5. Is the non-506B PMC clear, concise and not subject to interpretation?
6. What type of data or report is required to fulfill the non-506B PMC?

Q3. What if the applicant volunteers to conduct a PMC?

A3. Evaluate whether the commitment would provide pertinent regulatory information.

- If the review committee agrees with the commitment, then it is a non-506B PMC and should be included in the approval letter.
- If the review committee does not agree with the commitment, notify the applicant that the commitment is considered unnecessary but can be a voluntary study. Do not include the commitment in the approval letter.

Note: If a pending advice or an information request was discussed prior to an approval action yet was not formally included in an approval letter as a commitment, then identify the submission type as a Product Correspondence. the Regulatory Project Manager (RPM) should inform the applicant that the submission was incorrectly identified as a commitment and the Division should discuss the status and the disposition of the submission.

Q4. What information must be included in a non-506B PMC?

A4. CBER and the applicant mutually agree upon the WHAT and WHEN.

1. WHAT
 - a. ...does the reviewer want the applicant to study or perform?
 - b. ...does the reviewer want the applicant to submit to fulfill the non-506B PMC?
 - i. If it is a study, did you define the data you wish to be submitted?
NOTE: Requesting a study and submission of the data are ONE non-506B PMC
2. WHEN (is the non-506B PMC considered fulfilled)?

To ensure appropriate PMC tracking within CBER, enter the calendar date for when the non-506B PMC is expected to be fulfilled.

 - a. Include an actual date. **NOTE:** When negotiating milestones, it is

recommended to use the last day of a month as the due date. (i.e. May 31, XXXX).

- b. If an actual date cannot be determined, provide an estimated date.
NOTE: The “when” helps provides a framework for following up on whether or not the non-506B PMC was fulfilled, and provides a measure for inspectors to reference.