
OFFICE OF NEW DRUGS

Procedures and Responsibilities for Developing Postmarketing
Requirements and Commitments

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PURPOSE

- The purpose of this MAPP is to:
 - Define postmarketing requirements and commitments (PMRs/PMCs) and describe the policies and procedures to be used by the Center for Drug Evaluation and Research (CDER) staff to develop them.
 - Provide documentation of the PMR/PMC processes, roles, and responsibilities. The policies and procedures included in this MAPP span the time frame from reviewer identification of an issue in a drug application under review that could potentially lead to a PMR/PMC to the time the PMR/PMC is documented in the signed drug approval letter or postapproval PMR/PMC letter.¹
 - Improve consistency in the types of PMRs and PMCs that are required or agreed upon respectively across divisions and offices and across centers.
 - Improve clarity and transparency of CDER's decision-making process for PMRs/PMCs by ensuring that the rationale for the PMR/PMC is well-documented, the PMR/PMC is clearly described, and that good review management principles and practices (GRMPs) are followed in discussion of PMRs/PMCs with the applicant before the action goal date, and that similar principles and practices are followed after approval.

- This MAPP applies to the development of all reportable 506B PMCs for drugs and licensed biologics regulated by CDER, and to non-506B PMCs (i.e., chemistry,

¹ For the purposes of this MAPP, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

manufacturing, and controls and certain product stability studies) (see the Definitions section). This MAPP also applies to 506B PMRs for drugs approved under the Animal Efficacy Rule or accelerated approval, studies required under the Pediatric Research Equity Act (PREA), and safety studies or clinical trials required under the Food and Drug Administration Amendments Act (FDAAA). This MAPP describes the more common process of requiring or agreeing upon PMRs and PMCs respectively at the time of drug approval during the first review cycle, but it also applies to the development of PMRs/PMCs required or agreed upon during a subsequent review cycle or after approval.

- This MAPP does not address or describe the following topics. They will be addressed in other documents.
 - The drug-specific determination regarding whether a study should be conducted pre-approval or can be conducted as a PMR/PMC.
 - The type of study or level of evidence needed to fulfill a PMR/PMC.
 - The criteria for determining whether a postmarketing study or clinical trial should be a PMR or a PMC.²
 - Responsibilities for PMR/PMC tracking and review (i.e., after a PMR/PMC is issued). That topic is addressed in MAPP 6010.2 *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*.
 - The criteria for determining noncompliance with the conduct of PMRs or the required reporting for PMRs/PMCs.
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BACKGROUND

- Before March 25, 2008, PMCs were conducted by the applicant after the Food and Drug Administration (FDA) approved a drug for marketing or licensing, and were intended to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. These PMCs were either agreed upon by the FDA and the applicant, or required by the FDA under certain circumstances. Prior to the passage of FDAAA, the FDA required PMCs in the following situations:
 - Subpart H accelerated approvals (21 CFR 314.510 and 601.41), which requires postmarketing studies to demonstrate clinical benefit;
 - Deferred pediatric studies (21 CFR 314.55(b) and 601.27(b)), where studies are required under PREA; and
 - Animal Efficacy Rule Clinical Efficacy and Safety Studies (21 CFR 314.610(b)(1) and 601.91(b)(1)), where studies to demonstrate safety and efficacy in humans are required at the time of use.
- Section 130(a) of the Food and Drug Administration Modernization Act (FDAMA, 1997) amended the Federal Food, Drug, and Cosmetic Act (the Act) by adding a new provision requiring reports of certain postmarketing studies (section 506B of the Act (21 U.S.C. 356b)) for human drug and biological products. Section 506B of the Act provided the FDA with additional authority to monitor the progress of a PMC that an

² A guidance for industry on this topic will be developed in the future. Examples of PMRs and PMCs are provided in Attachment A.

applicant had been required or had agreed to conduct by requiring the applicant to submit a report annually providing information on the status of the PMC.³ This report must also include the reasons, if any, for failure to complete the commitment. This provision is implemented at 21 CFR 314.81(b)(2)(vii) and 601.70. Under section 506B(b) and (c), the FDA is required to track these PMCs, and report on them annually in the *Federal Register*.⁴

- In addition, new drug application applicants are required to report to the FDA on postmarketing studies/trials that are not 506B studies/trials under another section of the annual reporting requirements (21 CFR 314.81(b)(2)(viii)). Such studies or trials are not required, and they include chemistry, manufacturing, and controls studies that sponsors have agreed with the FDA to conduct (CMC commitments), and all product stability studies (stability studies). They also include “any postmarketing study not included under paragraph (b)(2)(vii) ... that is being performed by, or on behalf of, the applicant.”⁵ Reports on the status of these types of studies are not required reports under 506B.
- Effective March 25, 2008, section 901 of FDAAA created section 505(o) of the 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”.⁶ FDAAA at 505(o)(3)(B) states that studies and clinical trials may be required for one of three purposes:
 1. To assess a known serious risk related to the use of the drug;
 2. To assess signals of serious risk related to the use of the drug; or
 3. To identify an unexpected serious risk when available data indicate the potential for a serious risk

See the Definitions section for a definition of *studies* and *clinical trials* as they relate to the implementation of section 901 of FDAAA and this MAPP. Studies or clinical trials may be required under PREA (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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

- Attachment A describes the types of studies and clinical trials that would generally be considered to be PMRs under FDAAA as well as studies or trials that would be considered PMCs.
- The PDUFA IV Goals Letter requires the FDA to draft harmonized standard operating procedures between CDER and the Center for Biologics Evaluation and Research (CBER) by the end of fiscal year 2008. These procedures must articulate

³ See the guidance for industry *Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*, available at <http://www.fda.gov/cder/guidance/index.htm>.

⁴ <http://www.fda.gov/cder/pmc>

⁵ 21 CFR 314.81(b)(2)(viii).

⁶ Defined at section 505-1(b)(3) of the Act.

the FDA's policy and procedures for requesting PMCs (e.g., timing, content, rationale, and vetting process). When developing the procedures described in this MAPP, the FDA took into consideration the findings of the 2008 Booz Allen Hamilton study of current FDA procedures, as required under PDUFA IV.⁷ This MAPP includes procedures harmonized with CBER in a joint CDER-CBER working group and new FDAAA-related procedures for PMRs.

REFERENCES

- Federal Food, Drug, and Cosmetic Act, section 506B, and section 505(o)(3), created by section 901 of the Food and Drug Administration Amendments Act of 2007 (<http://www.fda.gov/opacom/laws/fdact/fdact5a.htm> and <http://www.fda.gov/oc/initiatives/advance/fdaaa.html>)
- 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/cder/guidance/index.htm>)
- Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (<http://www.fda.gov/cder/guidance/index.htm>)
- MAPP 6004.2 *Procedures for Completing and Processing the Form “Annual Report Review: Postmarketing Study Commitment Summary”* (<http://www.fda.gov/cder/mapp.htm>)
- MAPP 6010.2 *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments* (<http://www.fda.gov/cder/mapp.htm>)
- MAPP 6010.3 *Clinical Review Template* (<http://www.fda.gov/cder/mapp.htm>)
- MAPP 6010.8 *NDA and BLAs: Communication to Applicants of Planned Review Timelines* (<http://www.fda.gov/cder/mapp.htm>)
- Memorandum of Agreement between the Office of New Drugs and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (http://www.fda.gov/cder/drug/DrugSafety/OSE_OND_MOA.pdf)
- Postmarket Requirements and Commitments public Web site (<http://www.accessdata.fda.gov/scripts/cder/PMR/PMC/index.cfm>)

⁷ In 2006, the FDA commissioned a study by the consulting firm Booz Allen Hamilton of PMC-related processes as part of its continuous improvement effort for the drug and biologic review process. The study reviewed the PMC development process to identify ways to improve the decision-making process. The study report identified two main areas for improvement in the PMC development process: communication of the review issues and proposed PMCs to the applicant earlier in the review process, and increased consistency and transparency of the decision-making process through better documentation.

- Independent Evaluation of FDA's Prescription Drug User Fee Act III — Evaluations & Initiatives: Postmarketing Commitments Study Final Report (conducted by Booz Allen Hamilton beginning 2006, published January 2008) (<http://www.fda.gov/ope/PMC/pmc08.html>)

DEFINITIONS

- **506B-Reportable Postmarketing Commitments** — Postmarketing studies or clinical trials concerning clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology that applicants have agreed upon in writing or are required to conduct.⁸ Section 130 of FDAMA requires sponsors to submit annual status reports. The FDA is then required to make publicly available certain information about these studies/clinical trials.
- **Clinical Trial** — Any prospective investigation in which the sponsor or investigator determines the method of assigning the investigational product or other interventions to one or more human subjects.
- **Postmarketing Commitment (PMC)** — Any study or clinical trial that an applicant has *agreed*, in writing, to conduct after approval of a marketing or licensing application or supplement that is *not* a PMR (see below).
- **Postmarketing Requirement (PMR)** — Any study or clinical trial that an applicant is *required* to conduct after approval of a marketing or licensing application or a supplement. Studies or clinical trials may be required under PREA (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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).
- **PMR/PMC Development Coordinator** —
 - An Office of New Drugs (OND) review team staff member, generally the OND deputy division director for safety, who has been assigned the responsibility of reviewing PMRs/PMCs before they are sent to the applicant and before a letter issues.
 - Participates in decisions regarding established PMRs/PMCs (e.g., decisions to consider whether a PMR/PMC is released or fulfilled).
 - Reviews the PMR/PMC rationale to ensure that it is sound and clearly articulated, the PMR/PMC is feasible, and the schedule of milestones is

⁸ 506B reporting is described as *postmarketing study commitments*, even though some of these commitments are required under PREA and Subparts H, E, and I. Similarly, this reporting often refers to *study*; FDAAA distinguishes between study and *clinical trial*. Finally, 506B reporting includes *clinical safety* PMCs; studies or clinical trials that concern serious safety risks will now be required under FDAAA. Section 130 of FDAMA amended the Federal Food, Drug, and Cosmetic Act to add section 506B and predates FDAAA. The definition of postmarketing commitments has been revised in accordance with FDAAA.

appropriate. Refers concerns about these components to the review team and review management for discussion.

- **PMR/PMC Program Manager** — Person in the OND Immediate Office with PMR/PMC database and Web site oversight responsibility who ensures that all PMR/PMC-related information is updated and made publicly available in the appropriate data management systems. The PMR/PMC Program Manager also provides support and training to offices and divisions included on review teams; coordinates the development and revisions of PMR/PMC-related MAPPs, guidances, and other regulatory documents; and periodically updates senior and review management on implementation issues as needed.
- **PMR/PMC-Related Submission** — A formal submission sent by the applicant to address an established PMR/PMC. Such submissions may include:
 - PMR/PMC protocols
 - PMR/PMC correspondence
 - Annual status reports
 - Final reports
 - Supplemental applications submitted to address a PMR/PMC
- **PMR/PMC Schedule Milestones** — The specific milestone dates set forth as part of a PMR/PMC for conducting and completing a PMR/PMC that must be reported annually. The following milestone dates should be included in the schedule and in the letter when the PMR/PMC is required or agreed upon.
 - Final protocol submission date
 - Study/clinical trial completion date or time related 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 from completion)
- **PMR/PMC Tracking Coordinator** — One or more OND review division staff members, generally an OND review division safety regulatory project manager, with the role of ensuring that the review team is kept informed of PMC/PMR schedule milestones, verifying PMR/PMC information for accuracy, and monitoring whether expected activities are conducted according to the timelines specified in the letter and in CDER policy documents (e.g., applicant submissions and FDA review). The PMR/PMC tracking coordinator assumes primary responsibility for corresponding with the applicant regarding PMR/PMC **process** issues. The tracking coordinator's responsibilities generally occur after approval.
- **Quality Management Staff** — Staff in CDER's Office of the Center Director who initiate, conduct, and complete quality assurance assessments of Center-wide programs and processes.
- **Regulatory Project Manager (RPM)** — The OND division review team regulatory project manager (RPM) assigned to an application. The OND RPM has the primary

responsibility for coordinating with the review team and corresponding with the applicant regarding PMR/PMC **content** issues.

- **Reviewer** — Discipline reviewer assigned to a drug (e.g., clinical, clinical pharmacology, nonclinical toxicology, safety-related disciplines, quality, biostatistics).
- **Review Management** — For the purposes of this MAPP, is defined as supervisors (e.g., from OND, the Office of New Drug Quality Assessment (ONDQA), Office of Biotechnology Products (OBP), Office of Surveillance and Epidemiology (OSE), Office of Biostatistics (OB), Office of Clinical Pharmacology (OCP)) who oversee the work of members of the review team. In general, a review team member's team leader will be primarily involved in review oversight and will inform and consult with upper management, including the signatory authority, and other disciplines as needed, and will ensure that other disciplines are included on the team as needed.
- **Review Team** — All RPMs, reviewers, review team leaders, review management, and senior management in OND, ONDQA, OBP, OSE, OB, OCP, and others, who are responsible for drug application and submission review, both pre- and postapproval.
- **Review Team Leader** including the Cross-Disciplinary Team Leader (CDTL) — A discipline review team member who provides secondary review for the primary discipline reviewer, or in the case of the CDTL, leads the review team for a drug.
- **Senior Management** — For the purposes of this MAPP, is defined as:
 - CDER Center Director or Deputy
 - CDER super-office directors and deputies, including but not limited to those from OND, OSE, Office of Pharmaceutical Science, and Office of Translational Sciences
- **Signatory Authority** — For the purposes of this MAPP, is defined as individuals with authority to sign regulatory letters related to PMRs/PMCs.
 - OND review office directors and their deputies (i.e., Offices of Drug Evaluation (ODEs) I, II, and III; Office of Antimicrobial Products (OAP); Office of Nonprescription Products (ONP); and Office of Oncology Drug Products (OODP))
 - Division directors and their deputies (i.e., all OND review divisions under ODEs I, II, and III; OAP; ONP; and OODP)
- **Studies** — All investigations other than clinical trials as defined above, such as investigations in humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

POLICY

- All PMRs/PMCs will be developed and communicated using a standardized process.

- CDER review teams will meet, if possible, the GRMP-recommended timeline for communicating information about PMRs/PMCs to the applicant (MAPP 6010.8).
- CDER review teams will communicate to the applicant review issues that may lead to PMRs/PMCs and will do so as early as possible in the review process to facilitate discussion of these issues before the action goal date.
- CDER will review the rationale for each PMR/PMC and document each rationale in the PMR/PMC Development Template (see Attachments B and C). All safety studies and clinical trials will be PMRs (see Attachment A). PMCs that must be agreed upon between the FDA and the applicant will be requested only if the objectives are important to further the knowledge of the effective use of the drug and the PMCs do not fit the criteria for PMRs.
- The PMR/PMC development coordinator will review the decisional process leading to each PMR/PMC for drugs within his or her OND review division to ensure the process is consistent with the PMR/PMC decision process for all PMRs/PMCs within the OND review division, and will ensure that decision making has included all necessary disciplines.
- PMR/PMC development coordinators in each OND review division will develop best practices as a group to increase consistency, and will work with review management across offices throughout CDER.
- The PMR/PMC development coordinator will review each PMR/PMC for drugs within his or her OND review division to ensure that the PMR/PMC is clearly written and will result in timely submission of the appropriate data to address the issue that prompted the PMR/PMC.
- CDER will not require or agree upon PMRs and PMCs respectively for studies/clinical trials that are covered by other regulations (e.g., safety data updates or routine adverse event reporting) except in specific circumstances where an exception needs to be made. In those situations, the rationale for the exception will be documented in detail (following the PMR/PMC Development Template in Attachments B and C) and archived.
- CDER will work with the applicant as much as possible on the proposed schedule milestones to reach agreement. However, for PMRs under FDAAA, if CDER and the applicant cannot reach agreement, CDER may require the schedule milestones.

RESPONSIBILITIES AND PROCEDURES

Tables 1 through 7 outline the procedures and responsibilities by role for steps in the development and decision-making process for a PMR/PMC.

- Table 1 summarizes the overall responsibilities for staff responsible for developing PMRs/PMCs.

Table 1. PMR/PMC Overall Responsibilities

Role	Responsibility
Senior Management	<ul style="list-style-type: none"> • Ensures that the PMR/PMC development process steps, as defined in this MAPP, are implemented consistently across CDER • Provides an opportunity for review management to share updates on PMR/PMC development process issues or changes on a periodic basis
Signatory Authority	<ul style="list-style-type: none"> • Ensures that designated roles, particularly of the PMR/PMC development coordinator and tracking coordinator, have been assigned. • Ensures that all relevant disciplines and offices have discussed the content of the PMR/PMCs. • Describes the rationale for each PMR/PMC to provide historical background for future reviewers who may be reviewing PMR/PMC-related submissions for the drug or considering PMRs/PMCs for related drugs. This responsibility is addressed by completing the PMR/PMC Development Template for <u>each</u> PMR/PMC and including these templates in the Action Package. • Signs the letter.
Review Management	<ul style="list-style-type: none"> • Ensures that designated roles, particularly of the PMR/PMC development coordinator and tracking coordinator are clearly understood by all members of the review team • Ensures that staff are aware of standardized policies and procedures regarding PMR/PMC development and work with review team members and their supervisors to ensure that staff adhere to the standardized policies and procedures • Receives periodic updates on PMR/PMC status for drugs within his or her respective office or division • Ensures that the review team collaborates with other CDER offices as relevant to the PMR/PMC subject matter, to incorporate relevant input regarding rationale and other scientific issues • Reviews the rationale for requiring or agreeing upon each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority) • Provides concurrence on PMRs/PMCs before the letter issues
PMR/PMC Development Coordinator	<ul style="list-style-type: none"> • Ensures that the review team included all disciplines and offices relevant to the PMR/PMC subject matter • Ensures that the PMR/PMC description clearly communicates the objectives of the PMR/PMC so it can be adequately addressed by the applicant • Provides concurrence on the list of draft PMRs/PMCs before it is sent to the applicant and the final list before it is included in the letter • Ensures that the applicant has justified the choice of submitted schedule milestones

continued

Table 1, continued

Role	Responsibility
PMR/PMC Development Coordinator <i>(continued)</i>	<ul style="list-style-type: none"> • Ensures that the final schedule milestones are both feasible and reasonable • Ensures that the review staff resolves differences with the applicant, if any, between the objectives and schedule milestones set forth in the draft and final PMRs/PMCs • Assists as needed in documenting the rationale for each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority) • Ensures that PMRs/PMCs are applied consistently for drugs in his or her division • Ensures that development of PMRs/PMCs meets general policy guidelines in this MAPP • Supports and/or participates in a forum (e.g., quarterly meeting of all PMR/PMC development coordinators) where PMRs/PMCs are reviewed for lessons learned and consistency across CDER
Review Team Leader/CDTL	<ul style="list-style-type: none"> • Ensures that the PMR/PMC development and communication procedures are followed by the review team (e.g., timely notification of PMR/PMC review timelines, assists as needed in the use of the PMR/PMC Development Template) • Ensures that all appropriate disciplines and offices participate in the analysis and discussion of PMRs/PMCs • Reviews and provides concurrence for, or modifications of, the draft and final PMRs/PMCs proposed by primary reviewers before they are sent to the PMR/PMC development coordinator for final concurrence • Reviews proposed and final schedule milestones • Assists as needed in documenting the rationale for each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority)
Reviewer	<ul style="list-style-type: none"> • Identifies potential PMR/PMC review issues and works with the review team and review management to discuss these issues and communicate them to the applicant. • Recommends other discipline participation. • Participates in the analysis and decisions about PMRs/PMCs. • Creates a list of potential PMRs/PMCs and circulates it to the team leader, then the review team and PMR/PMC development coordinator for review and concurrence before communication to the applicant by the RPM. Ensures that the PMR/PMC description clearly communicates the objectives of the PMR/PMC. • Reviews and resolves any differences in the objectives and schedule milestones listed in the list of draft PMRs/PMCs compared to the list of final PMRs/PMCs. • Assists as needed in documenting the rationale for each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority)

continued

Table 1, continued

Role	Responsibility
Regulatory Project Manager	<ul style="list-style-type: none"> Provides the applicant with the communication timelines for when PMR/PMC discussions are tentatively planned to begin (MAPP 6010.8) Sends the draft PMRs/PMCs to the applicant as specified in the GRMPs Ensures that each PMR/PMC is numbered sequentially in the FDA letter Checks postapproval to ensure that the PMR/PMC database is populated with the PMRs/PMCs, including the schedule milestones Coordinates review-specific communications (e.g., protocol review comments from the review team) between the applicant and the review team for PMR/PMC content-related issues (pre- and postapproval)
PMR/PMC Program Manager	<ul style="list-style-type: none"> Provides process support and training to the offices and divisions in the review teams Supports continuous process improvement by coordinating the development of additional guidance as well as updates to appropriate MAPPs, as needed Provides status of process implementation to senior management and review management on a periodic basis
PMR/PMC Tracking Coordinator	<ul style="list-style-type: none"> Once a PMR/PMC is entered into the PMR/PMC database, assumes tracking responsibilities for the PMR/PMC until it is released or fulfilled according to MAPP 6010.2
Quality Management Staff	<ul style="list-style-type: none"> Conduct periodic process audits to determine compliance with the policies and procedures described in this MAPP

- Table 2 outlines initial steps for internal discussion once a potential PMR/PMC review issue has been identified, but a decision about whether a PMR or PMC is needed has not been made. A reviewer from any discipline may identify a potential PMR/PMC review issue and should discuss it with his or her team leader, the CDTL, and the rest of the review team. The team may first request clarification or additional information from the applicant before a final decision on a PMR/PMC is made.

Table 2. Identifying Potential PMR/PMC Review Issues for Internal Discussion and Informing Applicant of Potential Issues

Role	Responsibility
Reviewer	<ul style="list-style-type: none"> Identifies potential PMR/PMC review issues and discusses with the review team, review team leader/CDTL, and review management; determines how the issues should be communicated to the applicant (i.e., as a potential PMR/PMC or a request for more information) Collaborates with other CDER offices as relevant to the PMR/PMC subject matter
Review Team Leader/CDTL	<ul style="list-style-type: none"> Ensures that potential PMR/PMC review issues are discussed internally before the date specified in the 74-day filing letter Collaborates with other CDER offices as relevant to the PMR/PMC subject matter

continued

Table 2, continued

Role	Responsibility
Review Team Leader/CDTL (continued)	<ul style="list-style-type: none"> Participates in discussions of the review issues and how they should be communicated
Review Management	<ul style="list-style-type: none"> Ensures that potential PMR/PMC review issues are discussed internally, preferably starting at mid-cycle before the date specified in the 74-day filing letter Collaborates with other CDER offices as relevant to the PMR/PMC subject matter Participates in discussions of the review issues and how they should be communicated as appropriate Ensures that the scientific basis for the potential PMR/PMC is sound
PMR/PMC Development Coordinator	<ul style="list-style-type: none"> Provides input to potential PMR/PMC review issues being discussed by the review team, including the scientific rationale, as needed
Regulatory Project Manager	<ul style="list-style-type: none"> Communicates potential PMR/PMC review issues between the applicant and the review team as soon as possible in the review cycle

- Table 3 describes the procedure after initial discussion and review of any additional submitted information from the applicant results in a decision to require or request a PMR/PMC.

Table 3. Deciding PMR/PMC Is Necessary and Preparing Draft PMR/PMC

Role	Responsibility
Reviewer	<ul style="list-style-type: none"> Decides, in consultation with the review team and review management, whether PMRs/PMCs are necessary. Drafts a description of the PMRs/PMCs, ensuring that the description clearly communicates the objective and necessary study design details for applicant review, then provides the drafts to the team leader/CDTL, then the review team and PMR/PMC development coordinator for concurrence. Documents draft PMRs/PMCs and their rationale in the written review, consistent with the Clinical Review Template. Tells the applicant to submit schedule milestone dates with justification. Alternatively, prepares proposed PMR/PMC schedule milestones. Revises draft PMRs/PMCs as needed based on feedback from the review team, team leader/CDTL, and PMR/PMC development coordinator.
Review Team Leader/CDTL	<ul style="list-style-type: none"> Reviews draft PMRs/PMCs and the stated objectives and schedule milestones (if proposed by reviewer(s)) for clarity and appropriateness Communicates PMR/PMC deficiencies and concerns, if any, to the reviewer(s) with comments Routes the PMRs/PMCs to review management and the PMR/PMC development coordinator for concurrence

continued

Table 3, continued

Role	Responsibility
PMR/PMC Development Coordinator	<ul style="list-style-type: none"> Reviews the draft PMRs/PMCs from each discipline reviewer for clarity, consistency, and feasibility (e.g., schedule milestones, if proposed by reviewer(s)) Provides comments to the CDTL if there are questions regarding the PMR/PMC consistency or need Provides concurrence for the list of draft PMRs/PMCs before the RPM sends it to the applicant
Review Management	<ul style="list-style-type: none"> Reviews the draft PMRs/PMCs and provides comment and concurrence

- Table 4 addresses sending the list of draft PMRs/PMCs to the applicant and the subsequent discussion. During this part of PMR/PMC development, the goals and objectives of the studies or clinical trials may be discussed and refined. Schedule milestones generally are proposed by the applicant and should be reviewed and evaluated by the review team.

Table 4. Providing Draft PMRs/PMCs to the Applicant and Discussing as Needed

Role	Responsibility
Regulatory Project Manager	<ul style="list-style-type: none"> Provides draft PMRs/PMCs to the applicant at or before the time specified in the 74-day filing letter
Reviewer	<ul style="list-style-type: none"> Works with the RPM, review team, and applicant to discuss PMR/PMC content If schedule milestones were not previously proposed to the applicant, reviews the applicant's milestones to determine if they are feasible and reasonable Addresses and resolves differences, if any, between the lists of draft and revised PMRs/PMCs and their schedule milestones
Review Team Leader/CDTL	<ul style="list-style-type: none"> Participates in discussions when PMR/PMC content and schedule milestones are discussed by the review team and applicant Ensures that differences, if any, between the lists of draft and revised PMRs/PMCs and their schedule milestones are addressed and resolved by the review team
PMR/PMC Development Coordinator	<ul style="list-style-type: none"> Participates in discussions when PMR/PMC content and schedule milestones are discussed by the review team and applicant Ensures that the review staff resolves differences, if any, between the lists of draft and revised PMRs/PMCs and their schedule milestones
Review Management	<ul style="list-style-type: none"> Participates in discussions when PMR/PMC content and schedule milestones are discussed by the review team and applicant as needed

Table 5. Providing List of Final PMRs/PMCs and Schedule Milestones

Role	Responsibility
Reviewer	<ul style="list-style-type: none"> Provides list of final PMRs/PMCs, including schedule milestones, to the review team leader(s)/CDTL, PMR/PMC development coordinator, and review management for final concurrence
Review Team Leader/CDTL	<ul style="list-style-type: none"> Provides concurrence for the list of final PMRs/PMCs, including schedule milestones, then routes the list to the PMR/PMC development coordinator and review management for final concurrence and inclusion in the letter by the RPM Assists as needed in documenting the rationale for each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority)
PMR/PMC Development Coordinator	<ul style="list-style-type: none"> Reviews final PMR/PMC description and schedule milestones for clarity, feasibility, and consistency with other similar PMRs/PMCs Provides concurrence for the list of final PMRs/PMCs, including schedule milestones, for routing to review management and inclusion in the letter by the RPM Assists as needed in documenting the rationale for each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority)
Review Management	<ul style="list-style-type: none"> Provides concurrence for the list of final PMRs/PMCs, including schedule milestones, for inclusion in the letter by the RPM Reviews the rationale for requiring or agreeing upon each PMR/PMC in the PMR/PMC Development Template (documented by the signatory authority)
Regulatory Project Manager	<ul style="list-style-type: none"> Receives list of final PMRs/PMCs Ensures that each PMR/PMC includes at a minimum all schedule milestone dates specified by this MAPP If unresolved issues are identified, sends list to the respective discipline reviewer for review and resolution Consults with the PMR/PMC Program Manager or PMR/PMC tracking coordinator as needed to review PMR/PMC description for appropriate wording and details Ensures that PMR/PMC development coordinator and review management concur with the list of final PMRs/PMCs

Table 6. Including PMRs/PMCs in Approval or PMR/PMC Letter

Role	Responsibility
Regulatory Project Manager	<ul style="list-style-type: none"> Ensures that each PMR/PMC is numbered sequentially in the letter Finalizes letter using the content and format specified in the standardized letter templates Ensures that the PMR/PMC tracking coordinator and the PMR/PMC development coordinator are provided a copy of the final FDA letter
Signatory Authority	<ul style="list-style-type: none"> Documents rationale by completing the PMR/PMC Development Template for each PMR/PMC and including the templates in the Action Package Signs letter

Table 7. Entering PMRs/PMCs into PMR/PMC Database

Role	Responsibility
Regulatory Project Manager	<ul style="list-style-type: none"> Ensures the letter is processed correctly in the appropriate electronic management system
PMR/PMC Program Manager	<ul style="list-style-type: none"> Ensures that the PMR/PMC data entry staff enter the final PMRs/PMCs description, schedule milestones, and other PMR/PMC properties into the PMR/PMC database according to established procedures and that all relevant fields are populated for tracking purposes
PMR/PMC Tracking Coordinator	<ul style="list-style-type: none"> Checks postapproval to ensure that the PMR/PMC database is populated with all PMRs/PMCs documented in the letter, including schedule milestones For PMRs/PMCs with dates that refer to other schedule milestone dates (e.g., study completion within X months of final protocol submission), ensures that once the first referenced date has occurred (e.g., final protocol submission) all subsequent dates are calculated and captured in the PMR/PMC database as actual dates and communicated as a reminder to the applicant

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

Attachment A: Examples of PMRs and PMCs Post-FDAAA

I. PMRs under section 505(o) generally would include, but not be limited to, the following:

- Observational pharmacoepidemiologic studies are generally studies designed to assess a serious risk associated with a drug exposure or to quantify risk or evaluate factors that affect the risk of serious toxicity, such as drug dose, timing of exposure, or patient characteristics. To facilitate interpretation of the findings, the studies should always have a protocol, should include a control group, and should test prespecified hypotheses. However, control groups may be omitted when there is a scientifically valid reason to exclude controls. For a solely descriptive study, instead of a prespecified hypothesis, the protocol for a descriptive study may include clearly stated objectives for describing the safety issue, including a defined upper bound for detectable risk, if applicable. Data sources for observational studies could include administrative health care claims data, electronic medical records, registries, prospectively collected observational data, or other sources of observational information.
 - Registries may be designed with different goals.
 - Registries established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required as part of a risk evaluation and mitigation strategy (REMS) under section 505-1(f)(3)(F). When part of a REMS, they are an element necessary for the safe use of the drug, and are not designed as a study with termination dates. These types of registries would not be required as a PMR.
 - A drug may be approved with a requirement for a registry that will collect data to be analyzed in a study required as a PMR (under section 505(o)(3)), outside of a REMS (section 505-1(f)(3)(F)). When a pharmacoepidemiologic study using registry data meets the statutory criteria for a PMR, the registry and the study will be required as a PMR.
 - A sponsor may voluntarily create a registry to serve as a repository for clinical data, such as an outcomes registry. Such a registry is not required as part of a PMR (section 505(o)(3)). However, if the FDA becomes aware of new safety information in the postapproval setting, the sponsor could be required to conduct a PMR study, which may utilize the registry data.

Examples of observational studies include pharmacoepidemiologic studies designed to:

- Estimate the risk of a serious adverse event or toxicity associated with use of a drug
- Provide estimates of absolute risk (e.g., incidence rates) for a serious adverse event or toxicity
- Obtain long-term clinical outcome data, including information about potentially rare serious adverse events, in patients taking the drug compared to patients not exposed to the drug
- Identify risk factors (e.g., patient characteristics, duration of drug use) associated with the occurrence of adverse events among patients exposed to specified drugs
- Compare pregnancy incidence, pregnancy outcomes, and/or child outcomes after patient drug exposure compared to patients who did not receive the drug

- Meta-analyses may be designed to evaluate a safety endpoint by statistical analysis of data from completed studies or clinical trials. A meta-analysis should use a prospectively designed study protocol and analysis plan with a comprehensive selection of relevant studies or clinical trials and appropriate statistical methodology.
 - Perform a meta-analysis of the occurrence of all-cause mortality, cardiovascular death, and cancer incidence and identify potential predictive factors in patients treated with the drug compared to control therapies in all completed randomized clinical trials that include the drug

- Clinical trials with a safety endpoint evaluated with prespecified assessments and adequately powered to analyze the serious risk identified by the FDA under section 505(o) would be considered PMRs. Although efficacy endpoints may also be evaluated, the trial should be powered to adequately assess the safety concern that gives rise to the requirement. Examples include *clinical trials* designed to:
 - Evaluate the occurrence of asthma exacerbations associated with an irritative component of inhalation treatments for asthma in a controlled clinical trial, where the increased risk of drug-related exacerbation has the potential to offset the effectiveness of the inhaled drug
 - Determine the incidence of myocardial infarction in patients treated with the approved drug in a follow-on trial after approval, using the original randomized population
 - Evaluate differences in safety outcomes between patients withdrawn from treatment after some period of treatment and patients who remain on the treatment (randomized withdrawal trial)
 - Evaluate the potential for Q-T prolongation in a thorough Q-T clinical trial
 - Measure growth and neurocognitive function in pediatric patients treated chronically with the drug⁹
 - Evaluate safety in a particular racial or ethnic group or vulnerable population such as the immunocompromised⁹
 - Evaluate the safety of the drug in pregnant women⁹
 - Evaluate drug toxicity in patients with hepatic or renal impairment⁹
 - Evaluate long-term safety of cell and gene therapy products depending on the type of vector used and the inherent risk of integration
 - Evaluate the safety of a drug in patients with HIV-1 co-infected with hepatitis C or B

- Safety studies in animals investigating specific end-organ toxicities, including, but not limited to, carcinogenicity and reproductive toxicity studies. Although in most instances these studies are completed prior to marketing approval, they may be conducted postapproval for certain drugs — for example, products intended to treat serious and life-threatening diseases.¹⁰ If conducted postapproval, these studies would be required under 505(o). Examples include studies designed to:

⁹ Patients are treated with the drug at a dose and schedule specified in the clinical trial protocol.

¹⁰ See the ICH S1A guidance for industry *The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065007.htm>).

- Assess carcinogenic potential in appropriate species (e.g., mice and rats)
- Assess the potential for reproductive toxicology in appropriate species (e.g., monkeys or rabbits)
- Examples of in vitro laboratory safety studies that would qualify as PMRs would be studies designed to:
 - Assess certain receptor affinities for any circulating or major metabolites, including conjugates, to evaluate the potential for off-target binding and resulting serious risk
 - Determine whether resistance to a drug has developed in those organisms specific to the labeled indication, resulting in increased serious risk
 - Define the mechanism of drug resistance for certain organisms
 - Assess the risk of cross-contamination between products that could result from sharing product-contacting equipment and parts
 - Validate the accuracy, precision, sensitivity, specificity, and robustness of an immunogenicity assay for a drug or biological product to assess an immunologic safety concern
- Pharmacokinetic studies or clinical trials that would be PMRs include those to evaluate the pharmacokinetics of the drug in the labeled population or in a subpopulation at potential risk for high drug exposures that could lead to toxicity. Examples include studies or clinical trials designed to:
 - Determine the optimal dose for maintenance therapy in patients with chronic renal disease, a population at risk for drug accumulation
 - Study the pharmacokinetic profile in a rodent model of hepatic dysfunction in order to evaluate the potential for toxicity in patients with liver impairment
- Studies or clinical trials designed to evaluate drug interactions or bioavailability when there are scientific data that indicate the potential for a serious safety risk. Examples include studies or clinical trials to:
 - Assess in vitro whether products are p-glycoprotein substrates and therefore could lead to increased drug concentrations and toxicity
 - Assess potential interactions of an approved drug with a frequently concomitantly prescribed medication
 - Evaluate whether multiple doses of an approved drug alter the metabolism of a sensitive CYP2C9 substrate
 - Evaluate bioavailability of an oral drug in the presence of food

II. Examples of postmarketing commitments that are not required under section 505(o)(3)

Generally, the following types of studies or clinical trials would not meet the statutory purposes for PMRs, but might be considered agreed-upon PMCs:

- Drug and biologic quality studies, including manufacturing, stability, and immunogenicity studies, that do not have a safety endpoint, such as studies designed to:

- Develop an optical rotation test, collect data on commercial batches, and use the data to update drug substance specification standards
- Evaluate immune response to concomitant vaccination(s) that are a part of routine U.S. immunization practice
- Pharmacoepidemiologic studies designed to examine the natural history of a disease or to estimate background rates for adverse events in a population not treated with the drug that is the subject of the marketing application.
- Studies and clinical trials conducted with vaccines, such as surveillance and observational pharmacoepidemiologic studies when data do not suggest a serious risk or signals of serious risk related to the use of the vaccine and when available data do not indicate the potential for serious risk, such as:
 - A surveillance study of cases of the infectious disease targeted by the approved vaccine occurring in vaccinated populations; conduct product-specific surveys and calculate product-specific rates of infectious disease within the monitored population
 - A clinical trial conducted with vaccines in which the objective is a further characterization of the safety profile and the primary endpoint is not related to a serious risk identified by the FDA under section 505(o) of the Act
- Clinical trials in which the primary endpoint is related to further defining efficacy, designed to:
 - Evaluate long-term effectiveness or duration of response
 - Evaluate efficacy using a withdrawal design
 - Evaluate efficacy in a subgroup

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC development coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: _____

PMR/PMC Schedule Milestones:	Final Protocol Submission Date:	<u>MM/DD/YYYY</u>
	Study/Clinical Trial Completion Date:	<u>MM/DD/YYYY</u>
	Final Report Submission Date:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct postapproval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created postapproval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it (check all that apply):**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation

- The trial will be appropriately designed to answer questions about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Attachment C: Sample PMR/PMC Development Template: Product Quality (CMC)

TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types.

PMC #1 Description: _____

PMC Schedule Milestones:	Final Protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>MM/YYYY</u>
	Other: _____	<u>MM/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:	Final Protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>MM/YYYY</u>
	Other: _____	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE.**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct postapproval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

2. Describe the particular review issue and the goal of the study.

3. [OMIT — for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)