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Postmarketing Commitments Study Final Report

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1. EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) evaluates new drug and biological products prior to approval for marketing in the United States, in order to ensure the products' safety and efficacy for human use. However, in some cases, even if FDA approves a product, some issues may remain unresolved. In these instances, FDA may request that a sponsor seeking approval of a new drug or biological product conduct a postmarketing study to provide additional information that is important but not necessary for market approval. In certain situations, postmarketing studies are required by FDA (e.g., clinical benefit studies for products subject to accelerated approval, clinical benefit and safety studies for products approved based on animal efficacy data, and safety and effectiveness studies in pediatric patients). Studies that FDA requires sponsors to conduct, or which sponsors agree to conduct, after FDA has approved a product for marketing are referred to as postmarketing study commitments (PMCs) or phase 4 commitments.[1] Typically, PMCs are identified during the application review process and, while these issues are important to define, they do not represent major unaddressed safety and efficacy concerns, but instead are intended to further refine the safety, efficacy, or optimal use of a product, or to ensure consistency and reliability of product quality. Other postmarketing studies that are conducted by sponsors on their own initiative, typically to seek approval for new indications or formulations, are not PMCs.

Under section 506B of the Federal Food, Drug and Cosmetic Act (the act)[2], sponsors of approved drugs and biological products that have entered into an agreement to conduct a postmarketing study must report to FDA annually on the status of the study until the study is completed or terminated. These status reports must be submitted annually until FDA notifies the sponsor, in writing, that the agency concurs with the sponsor's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.[3] Section 506B of the act also requires FDA to develop and publish in the Federal Register annually a report on the status of postmarketing studies that sponsors have agreed to conduct and for which they have submitted reports.

The FDA commissioned this study to identify possible improvements to its existing PMC processes.[4] This report includes a retrospective analysis of agreed-upon PMCs and the processes associated with their development, tracking, and review.

Study Overview

Although FDA and most sponsors are complying with the reporting requirements for PMCs under the Food and Drug Administration Modernization Act of 1997 (FDAMA), the Agency believes that it should proactively evaluate PMCs as an important component of its Critical Path Initiative. Of significance, PMCs may identify important postmarketing adverse events. FDA decides whether additional studies are required to support approval or whether they can be performed after marketing begins. To this end, the Agency commissioned this evaluation to determine if FDA is consistent in its PMC decision-making process. The objectives of this study were to:

- Conduct a retrospective analysis of PMCs associated with New Drug Applications (NDAs), Biologic License Applications (BLAs), and supplements
- Evaluate the consistency of the PMC processes (requiring, requesting, facilitating, and reviewing) within divisions/offices, across divisions/offices, and across centers

[1] In this report, PMCs that are agreed to by the sponsor will be referred to as agreed-upon PMCs and PMCs that are required to be conducted by the sponsor will be referred to as required PMCs.

[2] Status reports for postmarketing studies are required by FDAMA, which became law on November 21, 1997. Section 130(a) of FDAMA amended the act by adding a new provision requiring sponsors to submit reports of the status of postmarketing studies (section 506B of act, 21 U.S.C. 356b).

[3] See 21 CFR 314.81(b)(2)(vii) and 601.70.

[4] Unless otherwise specified, subsequent references in this document to PMCs refer to agreed-upon PMCs.

- Identify process inefficiencies or inconsistencies
- Evaluate the value of PMCs with respect to public health objectives
- Develop recommendations for improving the quality of the PMC processes.

The study was based on a cohort of all 245 original product and supplemental applications approved with agreed-upon PMCs between FY02 and FY05. These applications contained a total of 743 unique PMCs.[5] Data were collected from FDA systems and through interviews with FDA reviewers (e.g., Regulatory Project Managers (RPMs), Medical Officers) and sponsor companies. The cohort consisted of 184 NDAs (118 original and 66 supplements) and 61 BLAs (29 original and 32 supplements). Thirty percent of the applications had at least one PMC, with an average of three per product (range was from 1.2 for the Office of Nonprescription Products and the Division of Metabolism and Endocrinology Products, to 5.0 for the Division of Anti-Viral Products).

PMC Development

The NDA/BLA review process is divided into five phases, under the Good Review Management Principles and Practices (GRMPs) guidance[6]: 1) filing determination and review planning; 2) review; 3) advisory committee meeting preparation and conduct; 4) action; and 5) post-action. The PMC lifecycle spans the review phases, usually beginning when FDA identifies an issue or data gap in a product application and determines that the gap can be resolved through a PMC. After notifying the sponsor of the need for a postmarketing study and receiving agreement, the PMC is documented, usually in an approval action letter. After the product is approved, sponsors submit protocols for the PMC studies[7], annual reports, and final study reports. FDA tracks, monitors and reviews these submissions until the PMC is fulfilled or released.

PMCs can be developed throughout the product life cycle (from pre-submission to post-marketing), but development most often occurred during the product application review. Reviewers often identified issues leading to PMCs early in the review process, during the filing and planning or review phases. However, sponsors were typically not informed of PMC requests until the action phase, sometimes only days before the action date. The timing of sponsor notification sometimes left insufficient opportunity for sponsors to evaluate study feasibility, clarify rationale and/or propose alternative study designs to achieve the desired objective. Consequently, a sponsor's input was sometimes limited to proposing or modifying goal dates rather than study design. Further, late sponsor notification was associated with a greater number of delayed, terminated, or released PMCs.

For PMC development, FDA should encourage reviewers to aim to meet the current GRMPs milestone that PMC discussions begin three weeks prior to division sign-off. Encouraging reviewers to meet this milestone would provide sponsors the opportunity to properly assess feasibility and propose alternative study designs that may be more effective. If feasible, FDA should notify sponsors of potential PMCs sooner. For PMCs known early in the review, the mid-cycle review would be an appropriate goal for notifying sponsors of those PMCs requiring clinical studies. Early notification of PMCs would allow time for sponsors to develop a workable approach or prepare evidence regarding the necessity or feasibility of the study, without any commitment from FDA to drug approval or to the PMC request.

[5] The study did not include required postmarketing studies under the Pediatric Research Equity Act (PREA), accelerated approval regulations, or the animal efficacy rule or those not reportable under 21 CFR 314.81(b)(2)(vii) or 601.70) (CMC or voluntary studies).

[6] Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products, April 2005.

[7] In some cases, sponsors submit protocols while the application is still under review.

PMC Rationale

PMCs were most often requested based on a need for additional data or analysis for an expected or submitted study in the application (21 percent) that did not significantly impact the overall assessment of safety and efficacy to warrant delaying approval. The next most common rationales for PMC requests were potential safety signals (13 percent), underrepresented subpopulations (12 percent) and drug-drug interaction concerns (10 percent). Divisions/offices had a similar set of reasons for requesting PMCs, but therapeutic area differences influenced which reasons were cited most frequently in each division.

Divisions/offices understand what is appropriate for a PMC, despite a lack of formal guidance. Most sponsors and FDA reviewers indicated that the PMCs they were involved with were appropriately deferred to phase 4, rather than required as part of the original marketing application. This timing decision was often based on the product safety profile in conjunction with the target population for the therapy. Review designation was also a factor in the decision to request PMCs. In particular, those applications that were designated for priority review were more likely to have PMCs requested than standard review applications. The most frequent reason given for requesting a PMC rather than requiring a completed study for approval was that the issue required further definition but did not affect the determination of safety and efficacy (33 percent of PMCs). The next most common reasons were that the issue was only a theoretical concern (16 percent) and that long-term data were required (14 percent). There was no significant difference in the probability of having PMCs requested on applications that were approved in single or multiple review cycles, further supporting the notion that FDA review teams have applied consistent standards for issues that can be resolved as PMCs.

While both FDA and sponsors agreed on the justification for most requested PMCs, increased transparency of the PMC process would provide other stakeholders (e.g., public interest groups, Congress) the same insights. As part of the existing GRMPs program, FDA should create and publish guidance regarding PMC requests. This guidance would ensure the appropriate level of process consistency across divisions/offices, while still allowing for the variability associated with different therapeutic classes. As part of this guidance, FDA should also ensure that reviewing, approving, and workload allocation responsibilities are assigned and performed consistently at the division level. These practices would likely reduce the number of requested PMCs, relieve workload pressure and allow more time and flexibility for remaining PMC activities.

PMC Milestone Submission, Review and Tracking

PMC tracking and review is an important part of the PMC process, ensuring successful and timely completion of these commitments. For each PMC, FDA and sponsors agree upon significant milestones for study completion. For PMCs that are clinical studies, typical milestones include: protocol submission, patient accrual, study start, study completion, and final report submission. Sponsors submitted their protocols and final study reports by the milestone date 76 percent and 60 percent of the time, respectively. FDA reviewers met their goal dates for completing annual status report reviews (3 months) 53 percent of the time, and final study report reviews (12 months) 61 percent of the time. The main reason for failure to meet review goal dates was competing workload priorities.

The current status of a PMC is characterized by the progress made by the sponsor against the original study schedule and milestones. A PMC that is conducted entirely on schedule proceeds through the following general study lifecycle. All PMCs are initially classified as pending, which indicates that the study has not started and the patient accrual date has not yet passed. Once the study has begun, it is classified as ongoing until the FDA receives the final study report, at which time it is classified as submitted. At the time that FDA has reviewed the report and notified the sponsor that the commitment has been satisfied, the PMC is categorized as fulfilled. There are also three additional status categories for classifying PMCs that do not proceed on schedule or to completion. If the PMC misses a milestone date on the original study schedule, it is

identified as delayed until the milestone is met, even if FDA and the sponsor have agreed to a revised timetable. The commitment is considered terminated if the sponsor discontinues the study before its completion. If FDA agrees that the study should no longer be conducted or is no longer feasible and notifies the sponsor, the PMC is classified as released.

Among PMCs in the study cohort, 34 percent were completed and 66 percent remained open. Of the open commitments, 81 percent were progressing on schedule,[8] while the remaining 19 percent were delayed. The most common reason for delayed PMC status was difficulty with patient enrollment in clinical trials (29 percent of delayed PMCs). As mentioned earlier, late sponsor notification of PMCs was associated with delayed study status, likely due to insufficient time to assess feasibility and/or clarify study objectives or design. In some instances, FDA and sponsor companies agreed to revise the original study schedule due to unanticipated delays such as difficulties in developing an agreed-upon study protocol. However, the original PMC milestones were used to determine PMC status. This means that some PMCs were classified as delayed despite proceeding according to a schedule agreed to by both FDA and sponsor. Moreover, it gives the appearance of a greater number of PMCs for which the sponsor is not putting forth sufficient effort and FDA is not adequately ensuring compliance.

The FDA has taken limited action to address delayed PMCs and reviewers have generally not contacted sponsors regarding delayed PMCs in order to determine the reason for the delay. Until the FDA Amendments Act of 2007 (FDAAA) was enacted, there was limited enforcement authority available to deal with sponsor noncompliance in addressing certain PMCs, which FDA reviewers interviewed claim has led them to place a reduced emphasis on PMC activities compared to other priorities, such as meeting PDUFA goal dates. Review team staff turnover (e.g., Regulatory Project Managers, Medical Officers) also affected timely review because it significantly impacted the level of knowledge of and responsibility for PMC tracking and review. Finally, the status tracking systems are passive and can fall out of date when FDA review teams do not submit updates in a timely fashion. For example, there is no consistent mechanism to determine when a PMC should move from pending to ongoing status, and renegotiated PMC schedules were inconsistently noted in the internal databases, each of which may result in inaccurate assessment and limited awareness of PMC status.

In the current environment, improving PMC development practices is anticipated to have the largest impact on increasing PMC compliance among sponsors, because clearly-articulated feasible PMCs are more likely to be fulfilled in a timely manner. Beyond PMC development, there are several other potential opportunities for improvement related to PMC tracking and review. First, adopt a quality systems process to ensure PMC responsibilities are met and document monitoring occurs. Second, monitor the frequency of PMC database updates and prompt non-responsive teams to submit updates, including any renegotiated PMC schedules. Finally, capture renegotiated PMC study schedules in existing database fields accompanying the current status assessment to give a more accurate representation of PMC status. This could be accomplished by requiring reviewers to notify the PMC database manager when a new schedule has been agreed to, and displaying this new study schedule in the internal PMC database. Other options that should be explored include displaying the revised schedule on the public PMC website[9], and releasing a PMC after its study schedule is renegotiated, and creating a new one with the revised milestone dates.

[8] On schedule refers to PMCs classified as pending, ongoing, or submitted.

[9] The PMC website database (http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm) is updated quarterly and available for viewing by the general public. It is referred to as the PMC website in this report. The internal PMC databases (one each in CDER and CBER) are continuously updated and are referred to as the PMC databases. For this report, the PMC databases were queried for PMC status.

PMC Public Health Impact

FDA promotes and protects the public health by evaluating new drug and biologic products to ensure they are safe and effective. PMCs can play a critical role in promoting the public health by providing additional safety, efficacy and optimal use data while the product is available to the general public. Alternatively, PMCs could be detrimental, if they do not provide meaningful results that impact the use of the product and divert resources that could be used for other drug development by sponsors and review of other products by FDA. The public health impact was first assessed in this study by determining the number of PMCs that resulted in label changes, which have tangible benefit in expanding the education of risks, benefits, and optimal usage of marketed drugs. For those PMCs that did not result in a label change, the public health impact was assessed through FDA interviews. More than half (51 percent) of fulfilled PMCs assessed in the study cohort resulted in a label change. The most common reasons for the label change were validated safety and efficacy concerns (30 percent of fulfilled studies with a label change), validated drug-drug interaction concerns (18 percent), and expanded use in subpopulations (16 percent). Additionally, for those studies that did not result in label changes, there was a discernible public health benefit, such as confirming safety (33 percent of fulfilled studies without a label change), confirming both safety and efficacy (10 percent) or satisfying safety concerns (9 percent).

Sponsors generally agreed (86 percent) that the PMC program has a positive public health impact, through studies enhancing clinical safety, clinical efficacy, or optimal use of products. However, 50 percent of sponsors questioned the value and/or rationale of specific PMCs. These sponsors noted that in some cases, the studies were ongoing at the time of approval of the product, and the PMC was simply a mechanism to ensure the results were submitted to FDA. Others reported that the PMC supported a reviewer's academic interests. Sponsors were divided on whether or not conducting studies to fulfill PMCs impacted their ability to conduct new product research and development (R&D). They indicated that additional FDA enforcement would neither change the sponsor's approach to PMC fulfillment, nor increase the priority with which PMCs were addressed. Overall, evidence indicates that the PMC program positively impacts public health, but PMCs need to be used judiciously to ensure that only studies addressing important issues regarding safety, efficacy and optimal use are requested.

2. BACKGROUND, OBJECTIVES, AND SCOPE

Studies may be conducted by a sponsor after FDA has approved a product for marketing. These studies can be:

- Required by FDA
- Agreed to by FDA and sponsor.

The circumstances under which FDA would require a sponsor to conduct a postmarketing study include:

- Confirmatory trials to demonstrate the clinical benefit of a product following accelerated approval
- Pediatric studies for products not adequately labeled for children, required as part of the Pediatric Research Equity Act (PREA)
- Studies needed to confirm safety and efficacy in human subjects for products approved under the Animal Efficacy Rule.

Agreements with sponsors to conduct postmarketing studies can be reached either before or after FDA has granted approval to a sponsor to market a product. These PMCs are intended to further define the safety, efficacy, or optimal use of a product, or to ensure consistency and reliability of product quality (chemistry, manufacturing and controls (CMC) commitments). Under section

506B of the act,[10] sponsors of approved drugs and biological products that have entered into an agreement to conduct a postmarketing study must report to FDA annually on the status of the study until the study is completed or terminated. These status reports must be submitted annually until FDA notifies the sponsor, in writing, that the agency concurs with the sponsor's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.[11]

An agreed-upon PMC is typically derived from a gap in product information that FDA identifies in an application, but determines through a carefully deliberated process that resolving the gap is not a condition of approval. FDA notifies the sponsor of the issue prior to the completion of the product review—before the action letter is issued. The sponsor must notify FDA in advance of their agreement to conduct the study before it is described in the action letter, and once the sponsor agrees to the PMC, a submission date schedule is usually established. These dates typically address:

- Protocol submission
- Patient Accrual
- Study start
- Study completion
- Final study report submission.

The sponsor is required to report the status of the PMC in their annual report to FDA, which is due within 60 days of the anniversary of the product approval each year.[12] FDA reviews the annual report (typically within 3 months) and then updates the status in the PMC database. A final study report submission (which is typically reviewed within one year of receipt) will also trigger an update to the PMC database. FDA uses the PMC database status to display certain information on a public PMC Web site in order to meet its obligations for public disclosure of information under FDAMA.

2.1 Study Objectives

FDA commissioned this PMC study as part of its continuous improvement effort to the drug and biologic review process. The objectives of the study were to:

- Conduct a retrospective analysis of PMCs associated with NDAs, BLAs, and supplements
- Evaluate the consistency of the PMC processes (requiring, requesting, facilitating, and reviewing) within divisions/offices, across divisions/offices, and across centers
- Identify process inefficiencies or inconsistencies
- Evaluate the value of PMCs with respect to public health objectives
- Develop recommendations for improving the quality of the PMC processes.

This study reviewed the PMC development process (i.e., when issues are identified in a review and how they become PMCs). The purpose of this evaluation was to identify ways to improve the decision-making process that results in requested PMCs. The study also assessed the PMC tracking and review process (i.e., once a PMC is issued, how is the status tracked and how are submissions reviewed) to determine improvements to these processes that may result in better status tracking or an improved PMC completion rate.

[10] See footnote 2.
[11] See 21 CFR 314.81(b)(2)(vii) and 601.70.
[12] See 21 CFR 314.81(b)(2) and 601.70.

2.2 Study Scope

This study is focused on PMCs that are agreed to by sponsors and FDA and are reportable under 21 CFR 314.81(b)(2)(vii) and 601.70, including those addressing:

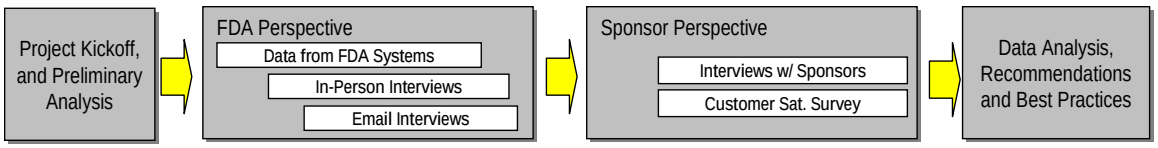
- Clinical Efficacy
- Clinical Safety
- Clinical Pharmacology
- Non-Clinical Toxicology

The source of the PMCs included in this evaluation were all NDAs, BLAs and supplements approved between FY2002 to FY2005. The study only focused on agreed-upon clinical efficacy, clinical safety, clinical pharmacology, and non-clinical toxicology PMCs in these approved applications (i.e., PMCs reportable under 21 CFR 314.81(b)(2)(vii) and 601.70). The decision to include only these PMCs was based on the assumption that they would provide the most relevant and useful additional information about the risks, benefits, and optimal use of an approved drug or licensed biological product. The study cohort excluded approved products that had only required PMCs or PMCs pertaining to CMC issues. For products with both required and agreed-upon PMCs, only the agreed-upon PMCs were reviewed, since the rationale for required studies is well-established in legislation.

3. METHODOLOGY

To ensure that the correct FDA systems and data sources were being accessed for the study, a preliminary analysis of ten product applications (seven NDAs and three BLAs) was conducted. After FDA reviewed and approved the preliminary analysis approach, the next step was to conduct the full analysis on the complete cohort of products. Data were gathered from FDA systems, FDA review team interviews and emails, and sponsor interviews and surveys. The findings from the preliminary and full analysis project phases were integrated for this final report. The high-level PMC study approach is illustrated below (Exhibit 1).

Exhibit 1. High-Level PMC Study Approach



FDA documents and databases were the initial source of information collected for each product and the associated in-scope PMCs. Many basic product and PMC attributes were consistently available from these sources, including:

- Product review details (e.g., approval date, sponsor company, FDA review division)
- Product review designations (e.g., priority/standard review, orphan designation)
- PMC descriptions and goal dates.

Some data that were found in FDA systems required further validation or was inconsistently available, such as:

- Rationale for requesting the study
- Description of why the review issue could be addressed as a PMC instead of a pre-approval requirement
- Timing of communication with sponsor to discuss potential PMCs
- PMC status
- Public health impact of completed PMCs.

FDA and sponsor interviews were conducted to confirm information found in FDA systems and to collect additional data. Interviews, both in-person and via teleconference, and surveys, via email,

were used to collect data in a structured format that facilitated aggregation and comparability between products and PMCs. To select the sponsors, FDA RPMs were asked to identify the appropriate sponsor point of contact with whom to discuss PMC development and status for their respective product. Of 110 sponsor companies represented in the study cohort, 51 companies were contacted via email to complete a customer satisfaction survey and 20 submitted responses to the survey.[13] Of these 51 sponsors, 39 were also invited to participate in a teleconference interview. A total of 18 sponsor interviews (i.e., nine biologic and nine drug products) were conducted in compliance with the Office of Management and Budget (OMB) guidelines. An interview handout or an OMB-approved customer satisfaction survey was provided to the sponsors who were interested in participating.

4. FINDINGS

The findings from this study are discussed in this section, organized by study cohort characteristics, PMC development, rationale, and tracking and review. These findings were derived from a combination of the data sources mentioned in Section 3, unless a particular source is noted.

4.1 Study Cohort Overview

The cohort contained all 245 original and supplemental applications[14] that contained agreed-upon PMCs, for both BLA and NDA products. Applications without agreed-upon PMCs were excluded from the analysis. The study cohort consisted of 48 percent original NDAs, 27 percent NDA supplements, 13 percent original BLAs, and 12 percent BLA supplements (Exhibit 2). Nearly half of the original NDAs were classified as New Molecular Entities (NMEs), while all original BLAs were considered NMEs. All BLA supplements were considered non-NMEs. The total number of unique[15] agreed-upon PMCs in this group was 743, for an overall average of 3.0 per application.[16] For both NDAs and BLAs, the average number of PMCs per application was significantly greater for NMEs than for non-NMEs.

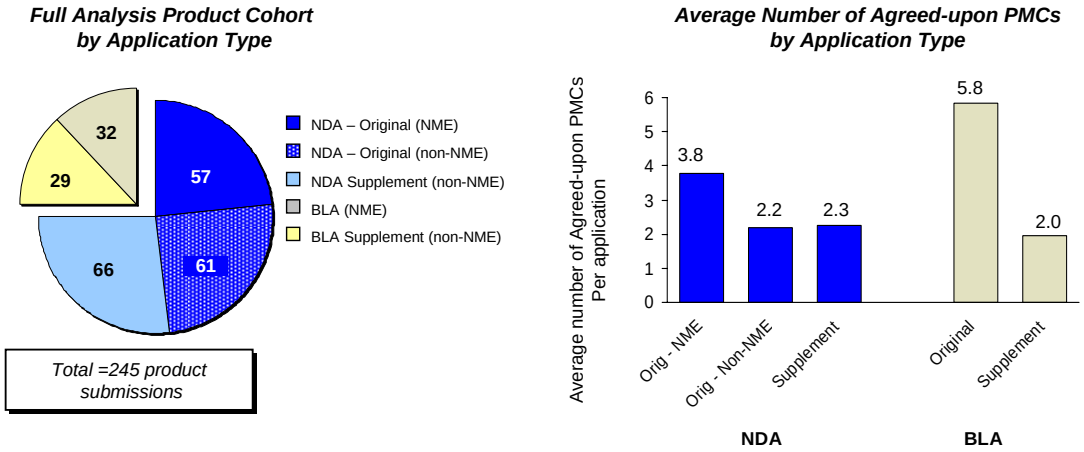
[13] There were a total of 42 individual survey responses because multiple people from the same company representing different products were contacted in some cases.

[14] The cohort included 275 total reviewed applications and supplemental applications. In some circumstances, FDA considered multiple applications (i.e., original applications and/or supplemental applications) during the same review cycle, issuing a single shared action letter and set of PMCs. For example the NDAs 21266 and 21267 were reviewed together and shared a single action letter with 4 PMCs. Of the 275 cohort applications, 30 products shared an action letter, thus leaving only 245 unique applications.

[15] PMCs issued on action letters with multiple applications were only counted once, hence all PMCs analyzed in this study are unique.

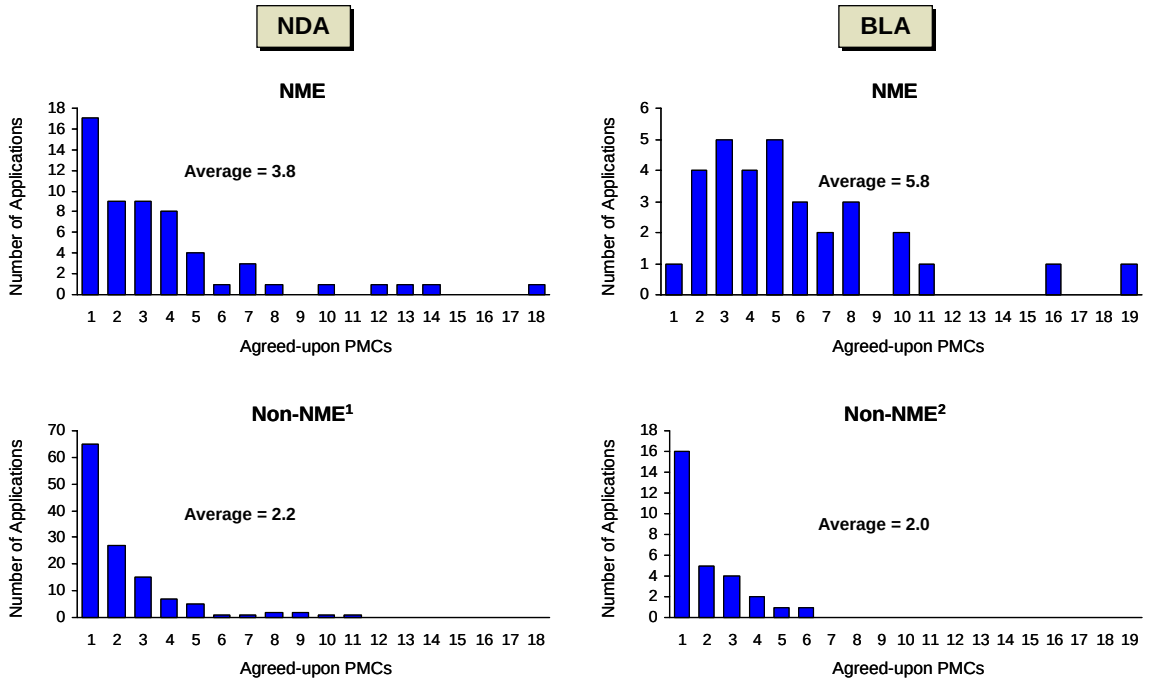
[16] Of the BLAs in the study cohort, 14 were in CBER and 47 in CDER. Among the BLAs in CDER, 22 were approved in CBER and transferred to CDER in 2003 during the drug and biological product consolidation, while the remaining 25 were approved in CDER.

Exhibit 2: PMC Study Cohort by NDA/BLA and NME/non-NME Status



The number of PMCs per application was more broadly distributed for NME applications than for non-NME applications (Exhibit 3). NME applications also had more outliers with significantly more PMCs than average.

Exhibit 3. Distribution of PMCs across BLAs and NDAs by NME/non-NME status

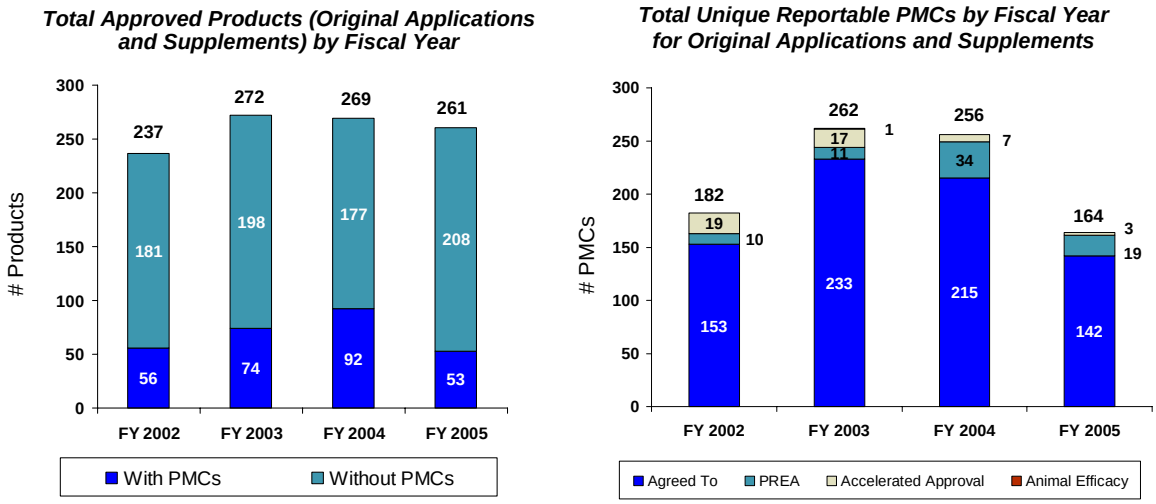


(1) Includes both original and supplement non-NME NDAs
(2) All non-NME BLAs are supplement applications

The number of product applications approved by year was relatively consistent, although the number of applications with PMCs dropped in FY05 after a steady increase during FY02 through

FY04 (Exhibit 4). The number of PMCs by year followed a similar pattern as the number of products with PMCs, demonstrating that the average number of PMCs per application remained consistent through the study cohort years.

Exhibit 4: Study Cohort Products and PMCs by Fiscal Year

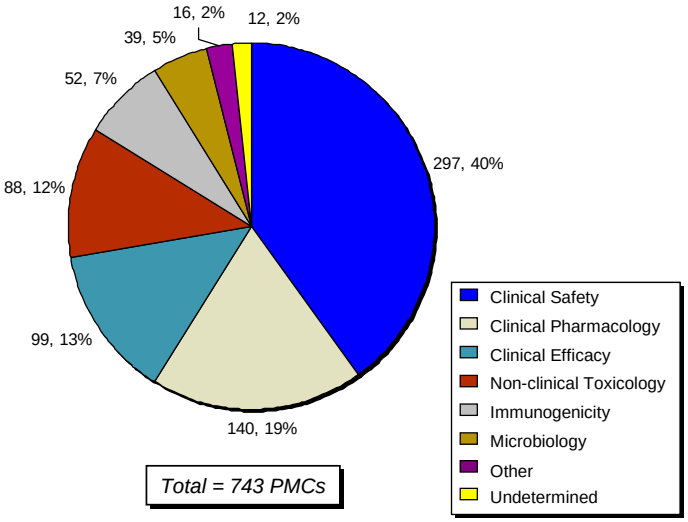


The PMCs in the study cohort were broadly categorized by study type. In addition to the four common types of PMCs described in the Code of Federal Regulations[17], two other study commitment types (immunogenicity and microbiology) were identified through interviews with FDA reviewers. The most common study category was clinical safety, which accounted for 40 percent of the PMCs in the cohort (Exhibit 5). The distribution of categories varied depending on the application type and NME designation. For example, clinical safety studies were more common in BLAs than NDAs and were more common in non-NME than NME applications. Non-clinical toxicology study commitments were more common in NDAs than BLAs. The proportion of clinical pharmacology commitments was greater in NME than non-NME applications, and they were much more common for NDAs than BLAs. As expected, microbiology studies were limited to antimicrobial NDAs, while almost all immunogenicity studies appeared in BLAs.

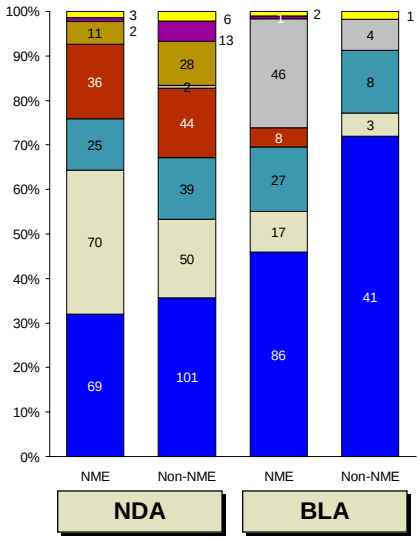
[17] 21 CFR 314.81(b)(2)(vii) and 601.70(a)

Exhibit 5: PMC Category Distribution

PMCs by Category

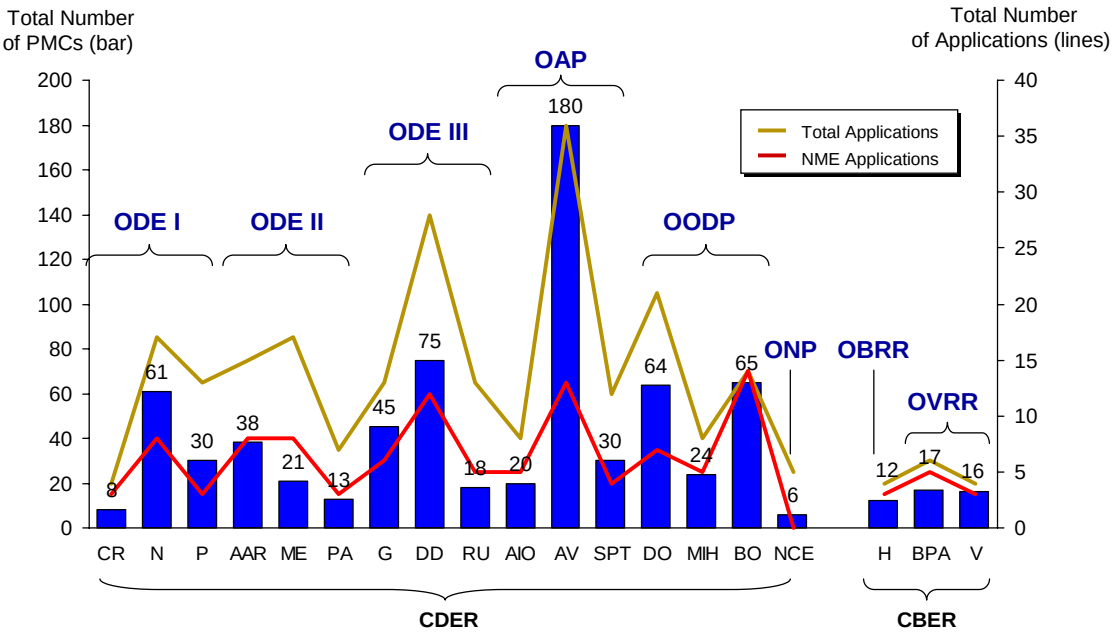


PMC Category by Application Type



The number of products reviewed and PMCs assigned varied considerably by FDA review division/office. Divisions with the most PMCs in the study cohort were Anti-Viral Products, Dermatology and Dental Products, Biologic Oncology Products, and Neurology Products (Exhibit 6). Those with the fewest products and PMC requests were Nonprescription Products and Cardiovascular and Renal Products. Divisions/offices with the most NMEs also tended to have more PMCs.

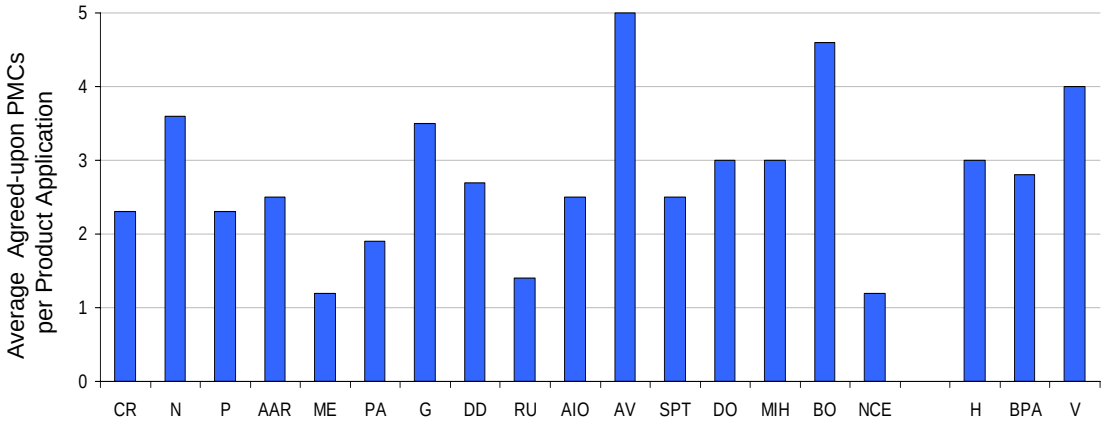
Exhibit 6: PMC and Product Distribution by Division, Office, and Center



Note: Excludes duplicate PMCs and products

The average number of PMCs per application ranged from a low of 1.2 for the Office of Nonprescription Products and the Division of Metabolism and Endocrinology Products, to a high of 5.0 for the Division of Anti-Viral Products (Exhibit 7).

Exhibit 7: Average Number of PMCs per Application by Division/Office[18]



	CR	N	P	AAR	ME	PA	G	DD	RU	AIO	AV	SPT	DO	MIH	BO	NCE	H	BPA	V
Mean	2.3	3.6	2.3	2.5	1.2	1.9	3.5	2.7	1.4	2.5	5.0	2.5	3.0	3.0	4.6	1.2	3.0	2.8	4.0
Min	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	3
Max	4	18	5	8	2	5	10	16	4	8	14	5	11	5	19	2	4	4	5
Mode	1	1	1	1	1	1	1	1	1	1	1	2	1	2	2	1	3	3	4

CDER **CBER**

Note: Only includes products with at least one agreed-upon PMC

4.2 PMC Development

The analysis of the PMC development process in this study focused on three primary concepts:

- The general implementation of the PMC development process
- The consistency in timing of each step in the process
- The impact of this timing on study outcome and status.

The NDA/BLA review process is divided into five phases, defined in the GRMPs guidance: 1) filing determination and review planning; 2) review; 3) advisory committee meeting preparation and conduct; 4) action; and 5) post-action. The PMC development process typically occurs during the application review, but in some cases begins prior to submission. In general, the process involves the following high-level steps: 1) the sponsor is notified of the issue/gap, 2) FDA decides that the gap can be addressed as a PMC, 3) the sponsor is notified of the PMC request, 4) the sponsor agrees to the PMC, and 4) the commitment is documented in the action letter (Exhibit 8).

The PMC development process is initiated when a data gap or issue is identified, which typically happens early in the review process. Eighty-two percent of issues were identified after application submission and before the end of the review phase. Twelve percent of issues were discovered prior to the submission and were inadequately addressed by the sponsor at the time of submission. Once an issue was identified, FDA occasionally notified the sponsor of the issue before making the decision to address it as a PMC; however, in many cases FDA did not discuss the gap in product information with the sponsor until after the PMC decision point. The PMC decision point occurred most often in the review phase (59 percent), but also occasionally in the action phase (23 percent). Despite this relatively early PMC decision point, sponsors were more likely to be notified of the PMC late in the review, during the action phase (65 percent), than in the review phase (33 percent). Late notification appears to have negatively impacted PMC progress and outcome, and is discussed further in Section 4.4.2.

[18] The legend for Exhibit 6 also applies to Exhibit 7.

Exhibit 8: PMC Development by GRMPs Phase

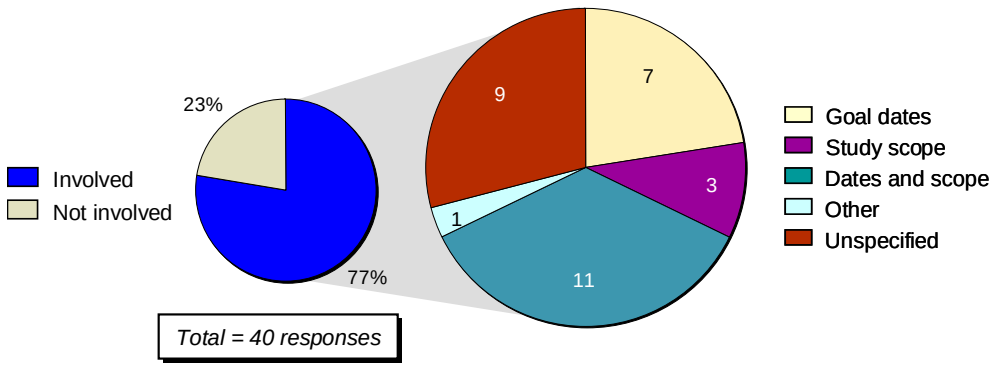
Development Milestone	Description	Pre-Submission	Filing & Planning (I)/ Review Phase (II)	AC Phase (III)	Action Phase (IV)	Total Responses
		Application Receipt			*Goal Date*	
Issue Identification	Gap is identified by reviewer	(n=24)	(n=171)	(n=9)	(n=4)	208
Sponsor Notified of Issue	Sponsor notified of review issue	(n=17)	(n=49)	(n=10)	(n=22)	98
PMC Decision Point	Decision that the issue can be resolved as a PMC, instead of as a pre-approval issue	(n=12)	(n=96)	(n=7)	(n=37)	152
Sponsor Notified of PMC	FDA sends PMCs to the sponsor, sometimes providing an opportunity to discuss scope and milestones	(n=3)	(n=46)	(n=0)	(n=90)	139
Sponsor Agreement	Sponsors send a letter of agreement to PMC and timeline for PMC completion	(n=0)	(n=28)	(n=0)	(n=102)	130
Action Letter	Final agreed upon PMCs are documented in the final Action Letter	(n=0)	(n=0)	(n=0)	(n=265)	265

0-5% *6-35%* *36-60%* *61-85%* *86-100%*

Note: Totals are different for each milestone phase because data for every PMC was not available for each milestone
Source: FDA interviews

Over 60 percent of the 18 sponsors interviewed requested that PMC discussions occur earlier in the review process to provide for sufficient time to evaluate the feasibility of a requested study or to verify and discuss the rationale in order to inform their study objectives and design. Sponsors indicated that they usually agreed to the studies in order to receive approval by the action date, but that rushed agreement had occasionally led to difficulties in subsequent study design and trial execution, with corresponding delays in PMC progress. More than three-quarters of FDA review teams interviewed reported that sponsors provided some input to the PMC, usually during the action phase. Sponsors were most often involved in setting goal dates but less frequently contributed in study trial design, usually because the timing of the interaction did not provide for adequate discourse with FDA (Exhibit 9).

Exhibit 9: Sponsor Involvement in PMC Development



Note: Sponsor involvement indicates a role in the development of any of the PMCs for a product
Source: FDA Interviews

4.3 PMC Rationale

In addition to analyzing the overall PMC development process, this study included an analysis of the rationale for assigning the PMCs. The rationale for each PMC in the cohort was characterized in two ways:

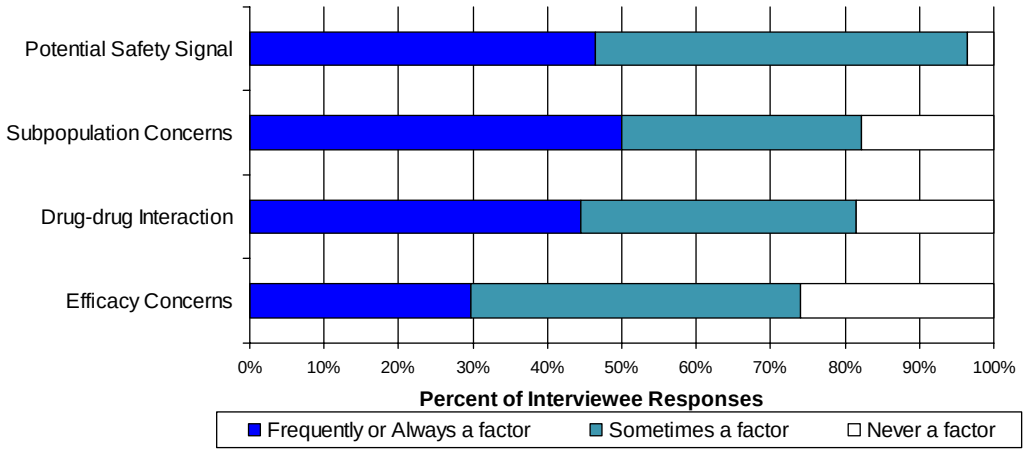
- What is the issue or data gap that needed to be addressed?
- What is the reason the issue/gap was appropriate for a PMC, instead of a requirement for approval (i.e., study timing)?

The goal was to capture the nuanced thinking that occurs during a review and the breadth of factors considered during the decision-making process.

4.3.1 Issue/Data Gap

When FDA reviewers were asked to generalize, the most commonly cited reasons for PMC assignment were: potential safety signals in submitted studies, underrepresented subpopulations, and drug-drug interaction concerns (Exhibit 10).

Exhibit 10: Factors that Influence FDA's Decision to Request a PMC[19]

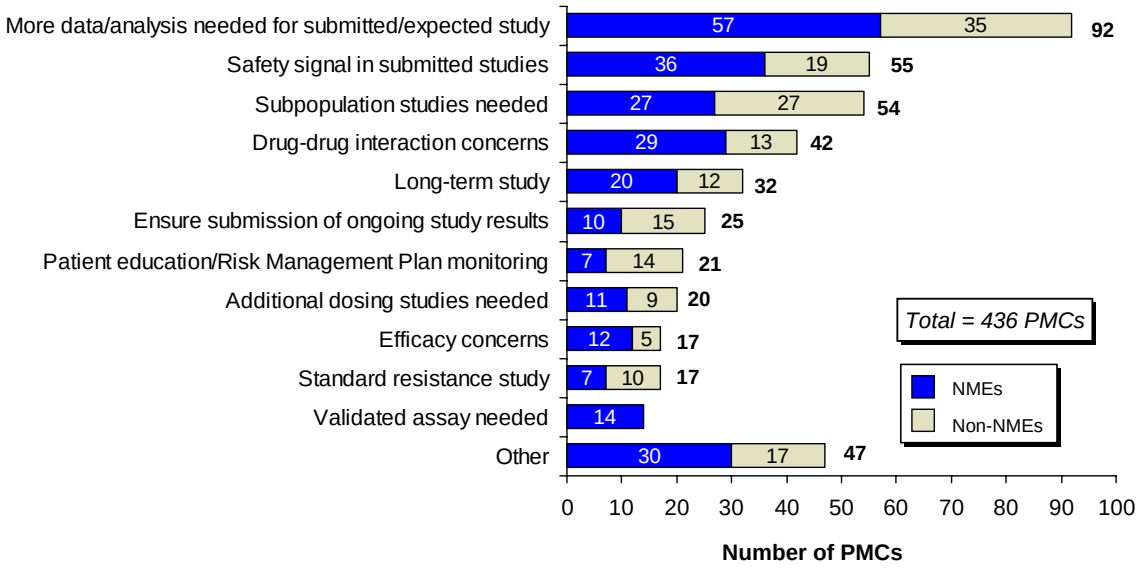


Review team perceptions were supported by the actual rationale given for individual PMCs in the study cohort. Interviewees most frequently cited that the rationale for assigning a specific PMC was a need for additional data or analysis for an expected or submitted study in the application (Exhibit 11)[20]. The next three most common reasons for requesting actual PMCs were potential safety signals in submitted studies, subpopulation studies needed, and drug-drug interaction concerns.

[19] During interviews with FDA product review teams, reviewers were asked to assess the frequency that certain specified factors influenced a PMC request. Data collected were qualitative and based on the review team's overall experience with PMCs.

[20] The rationale "Submitted/expected study insufficient or absent" was not included in the survey shown in Exhibit 10.

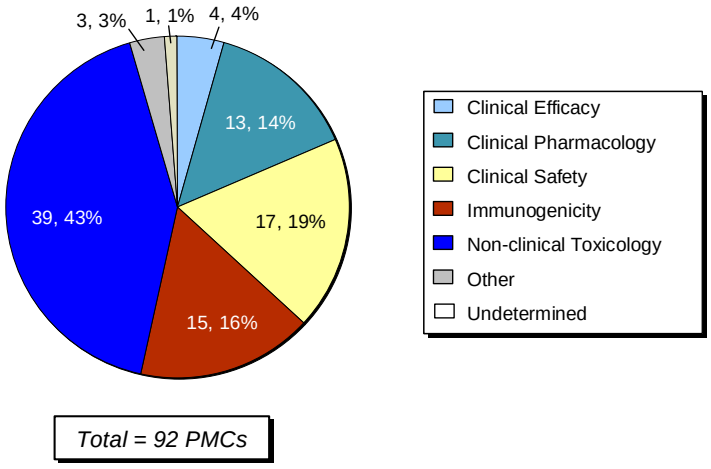
Exhibit 11: Actual PMC Rationale for FY 2002-2005 Cohort[21]



Note: Excludes 307 PMCs, for which the rationale was not determined
Source: FDA interviews

To further define the finding that a need for additional data or analysis for an expected or submitted study led to a PMC, the type of issue/gap was analyzed (Exhibit 12). Non-clinical toxicology studies were the most common study type to be requested based on this rationale, followed by clinical safety, immunogenicity, and clinical pharmacology.

Exhibit 12: Study Type Requested When Additional Data or Analysis Needed for Expected/Submitted Study



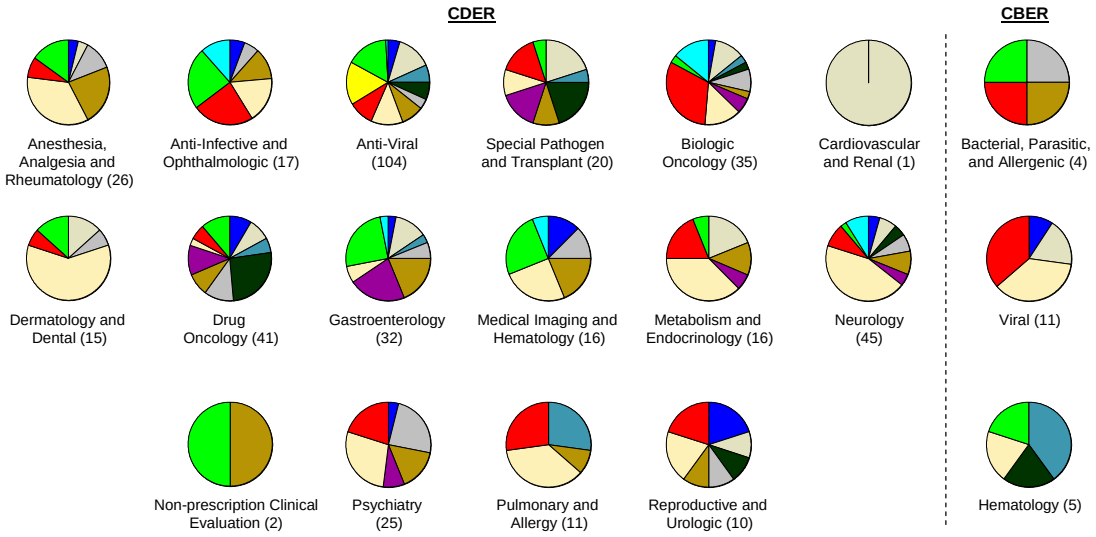
Source: FDA Interviews

While rationales were similar across review divisions/offices, the mix of rationales for PMCs within each division varied (Exhibit 13). Interviewees attributed these differences to therapeutic area

[21] The rationale was not determined for PMCs for which an FDA interview was not conducted or for which FDA interviewees could not recall the rationale.

differences or product-specific issues, rather than an inconsistency due to different decision-making processes. For example, resistance studies were typically requested for antimicrobial products, but are not relevant for other therapeutic areas. Similarly, assay validation was requested for immunogenicity studies for biologics, but almost never for drug products, which explains part of the reason for the greater number of PMCs associated with approved BLAs. Drug-drug interaction studies were more likely to be requested for products targeting conditions in which patients are likely to be taking several therapies at the same time, such as HIV and cancer. In general, the rationale for most PMCs, across all review divisions/offices, was determined by factors specific to each product application.

Exhibit 13: PMC Study Rationale by Review Division



Note: Excludes 307 PMCs, for which the rationale was not determined

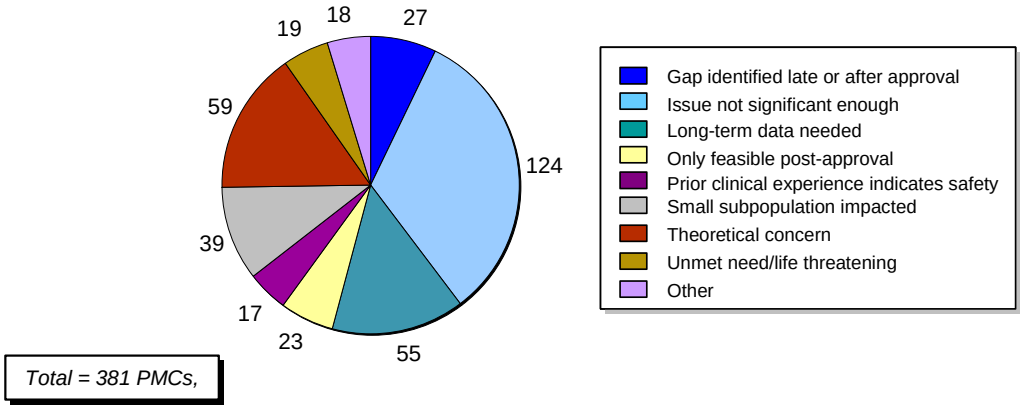
4.3.2 Study Timing

In addition to identifying an issue or data gap that must be addressed, reviewers had to determine whether it could be addressed as a PMC or needed to be resolved prior to approval. This was a complex and product-specific decision, influenced by factors such as the safety profile and target population of the product. FDA reviewers interviewed believed all PMCs in the study cohort were appropriate for post-approval studies. The four most commonly cited reasons for allowing post-approval rather than pre-approval timing were (Exhibit 14):

- **Not Significant Enough:** The lack of information was not important enough to cause the product not to be considered safe or effective, but was important to know for the optimal use of the product.
- **Theoretical Concern:** The issue was not identified from information supplied in the product application, but was based on the reviewer's experience (e.g., prior experience with drugs in that class, knowledge of common adverse events for that disease, anticipated off-label use of the product).

- **Long-Term Data:** The issue required long-term data, generally five or more years worth of product use, which was not practical to collect prior to product approval.
- **Small Subpopulations**: The issue was expected to impact a small subpopulation of the users; this concern was sometimes noted on the product labeling.

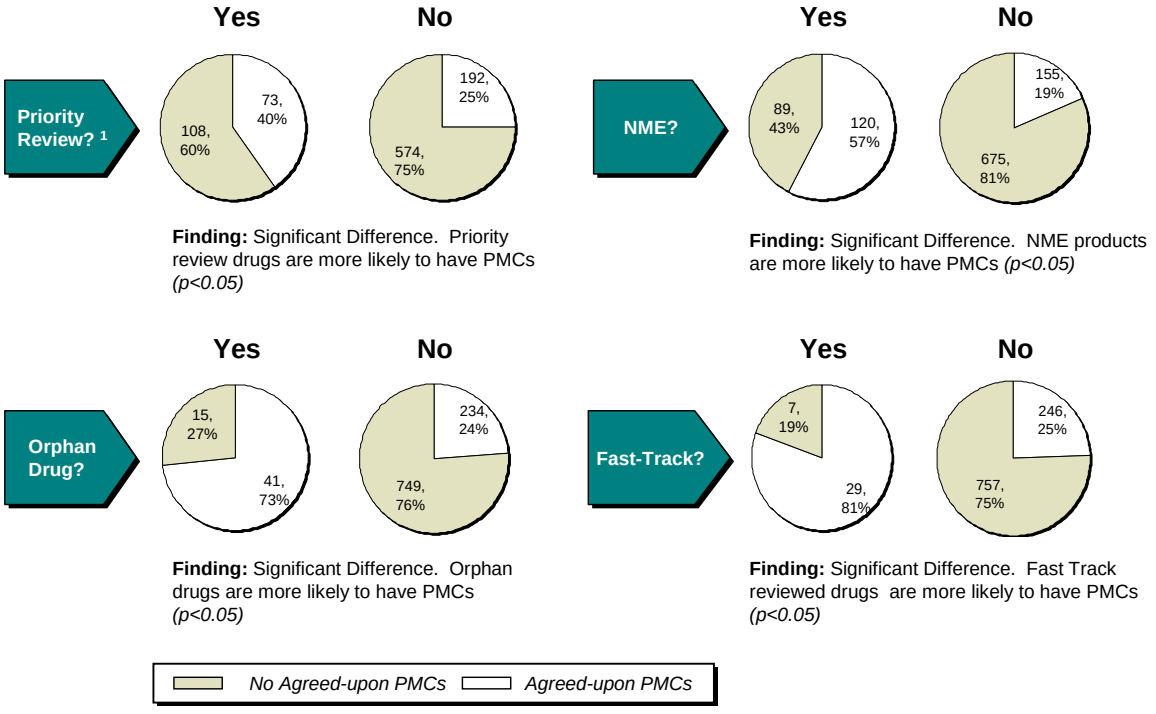
Exhibit 14: Primary Rationale for Postmarketing Study Timing



Note: Excludes 362 PMCs, for which study timing rationale was not determined
Source: FDA Interviews

Several product review characteristics, related to product novelty or therapeutic area urgency, were examined for influence on study timing decision (Exhibit 15). Products designated as priority review, which are deemed to have the greatest potential for improvement over existing therapies, were significantly more likely to be approved with PMCs than standard review products. Fast track and orphan drugs, which address serious diseases and unmet needs and conditions impacting small populations, respectively, were also more likely to be approved with PMCs. The data suggests that reviewers take into account the potential benefit of a product when determining whether an issue can be resolved post-approval. NMEs in the study cohort were more likely to be approved with PMCs than were other chemical types, further supporting the idea that products with greater potential for significant therapeutic advance are more likely to receive PMCs to resolve review issues, rather than be addressed through a subsequent review cycle. Additionally, NMEs are likely to have more unknowns, which would also explain the greater number of issues to resolve in the postmarketing phase.

Exhibit 15: Influence of Product Review Factors on PMC Decision



Note: 1. Priority status was not determined for 82 products without PMCs and 10 products with PMCs

4.3.3 Best Practices Observed

Few divisions/offices had specified procedures surrounding PMC development, but several effective practices were noted. Some divisions/offices used a "PMC gatekeeper" to monitor the consistency of assigned PMCs before issuing the action letter. In addition to checking the clarity of the wording and the suitability of goal dates, the gatekeeper often ascertained if there were sufficient divisional resources to track and review the PMC submissions. Some review divisions/offices were more diligent in advising sponsors of issues that could lead to PMCs and others notified sponsors of PMC requests at GRMPs milestone meetings, allowing sufficient time for discussion and clarification.

4.4 PMC Milestone Submission, Tracking and Review

The PMC tracking and review process covers all activities after the PMC is agreed to and documented in the action letter. Sponsor activities often include submission of a study protocol, annual status report, and final report submission. FDA activities include review of sponsor-submitted materials, communication with sponsors as needed, and maintenance of internal tracking systems. Each area is investigated in this section, including factors contributing to delayed PMCs, timeliness of sponsor submissions, and timeliness of FDA review.

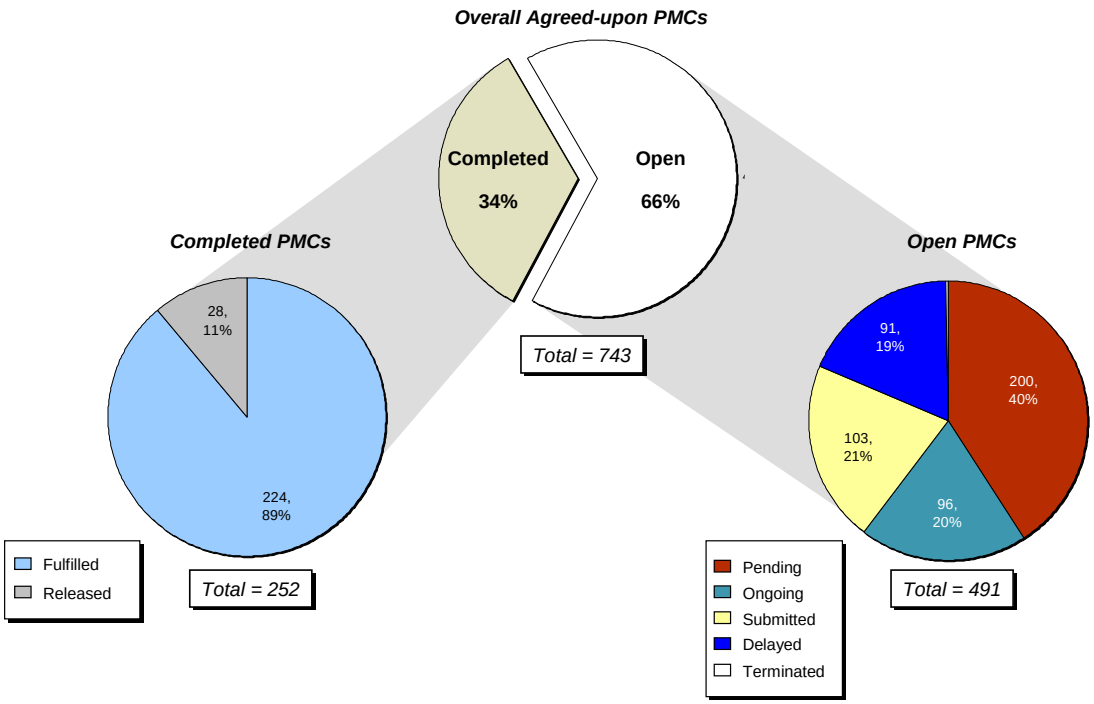
4.4.1 Status of PMCs in Study Cohort

In the study cohort, 34 percent of the PMCs were completed[22], while 66 percent remained open (Exhibit 16). Of the completed PMCs, 89% were fulfilled and 11% were released. Among the

[22] Completed refers to fulfilled or released commitments; Open refers to pending, ongoing, submitted, delayed or terminated PMCs

PMCs that were open, 81% were proceeding on schedule[23], 19% were classified as delayed, and one PMC was terminated.

Exhibit 16: Status of PMCs[24]



Sources: FDA interviews and tracking databases

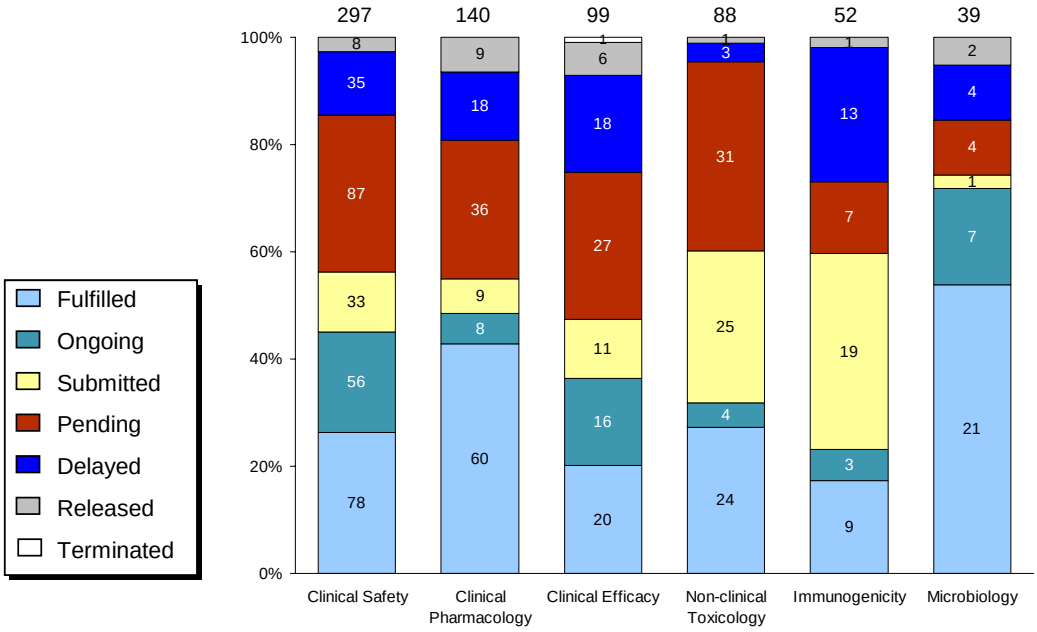
The mix of PMC status was similar across study types (Exhibit 17), with the status variations likely due to differences in the PMC milestone dates. For example, over half the microbiology PMCs have been fulfilled, which is the highest proportion for any study type in this cohort. This may be attributed to the fact that most microbiology PMCs were requested in the earlier years of the cohort period. As microbiology resistance studies have become standard components of anti-microbial product applications in recent years, fewer have been requested in the postmarketing phase because sponsors are submitting them in the NDA.

Very few non-clinical toxicology studies were classified as delayed, likely explained by two factors noted by FDA interviewees. First, most non-clinical PMCs were relatively straightforward studies compared to clinical studies, and second, there were no patient enrollment challenges, which were the leading cause of delayed commitments.

[23] On schedule refers to PMCs classified as pending, ongoing, or submitted.

[24] Analyses reflect the PMC status as of December 2006.

Exhibit 17: Status of PMCs by Study Type



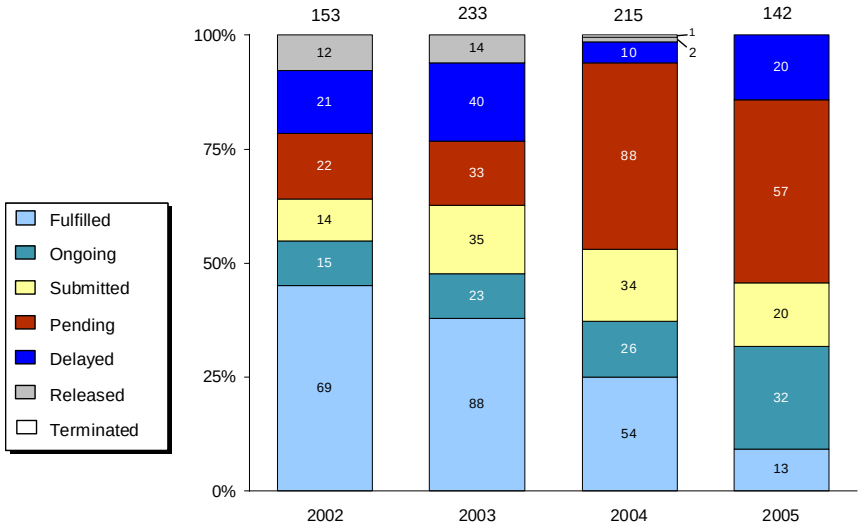
Note: 28 PMCs that do not belong in the six major categories are not shown (16 Other and 12 Undetermined)
Sources: FDA interviews and tracking databases

The distribution of PMC status across the cohort (Exhibit 18) differed from the status reported in the 2007 *Federal Register*[25], which can be explained by several factors. First, the time at which the status was assessed in this study was three months later than that in the *Federal Register*. Second, the *Federal Register* statistics includes certain PMC types excluded from this study, such as Accelerated Approval and PREA PMCs. Third, this study obtained updated status on PMCs through FDA interviews, while the *Federal Register* report relied solely on the PMC databases, which are updated only after the verification and review of information by FDA staff (Exhibit 21). Finally, this study was limited to a cohort of products approved between fiscal years 2002 and 2005, while the *Federal Register* report included all open PMCs.

Due to the nature and complexity of some clinical PMCs, the amount of time from product approval to PMC fulfillment often takes many years. In reviewing the PMC status of the cohort, there is an expected trend where there are more fulfilled older PMCs than newer PMCs. Newer PMCs are typically pending due to a lag between product approval and patient enrollment.

[25] Summary of Postmarketing Study Commitments (as of Sept. 30, 2006); *Federal Register*, Vol. 72, No. 22, p. 5069-5070. Feb 2, 2007.

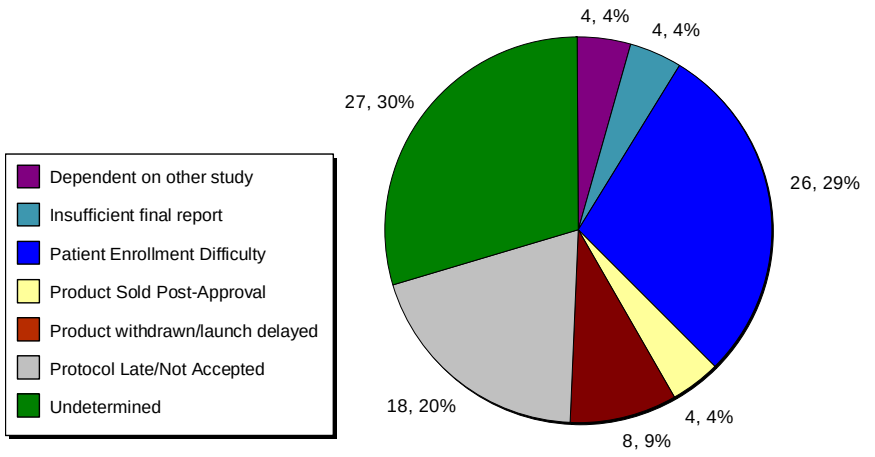
Exhibit 18: PMC Status by Fiscal Year of Product Approval



4.4.2 Factors Responsible for Delayed PMCs

The most common reasons for delayed PMCs were patient enrollment difficulties and late/unaccepted study protocol submissions (Exhibit 19). Some FDA reviewers speculated that the lack of an enforcement mechanism to deal with sponsor noncompliance influenced some sponsors to be less timely in completing their commitments.

Exhibit 19: Reasons for Delayed PMC Status

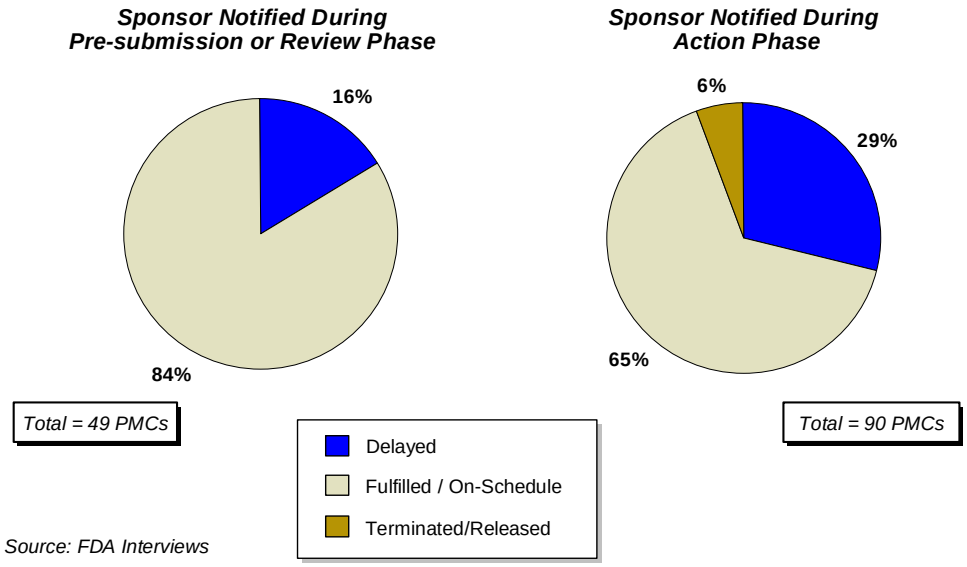


Source: FDA Interviews

Delayed PMCs were present in almost all study types and review divisions/offices, but one factor that appeared to contribute to the delayed status was the timing of sponsor notification of the PMC during the application review. As mentioned earlier (Section 4.2), most data gaps that became PMCs were identified early in the review, but sponsors were most often notified of the PMC request in the final weeks or days prior to the action date. In the study cohort, PMCs for which the sponsor was notified in the action phase were more frequently delayed than those in

which the sponsor was notified during the review phase or earlier (Exhibit 20). This observation is consistent with sponsor comments that late notification of PMC requests made it more difficult to evaluate study feasibility and contributed to the difficulty in meeting milestones on time.

Exhibit 20: PMC Status by GRMPs Phase of PMC Notification



Source: FDA Interviews

4.4.3 PMC Tracking and Communication

The FDA tracking process was driven by sponsor submissions. PMC status was checked and updated when a submission (either an annual report or final study report) was received and except for rare situations, there was no FDA follow-up on missed milestones.[26] Since, in general, sponsors were not asked to contact FDA when they started a study, there was no mechanism for the timely update of a PMC status from pending to ongoing, other than the annual status report that could be submitted months after the study began depending on the relative timing of the anniversary date of U.S. approval.

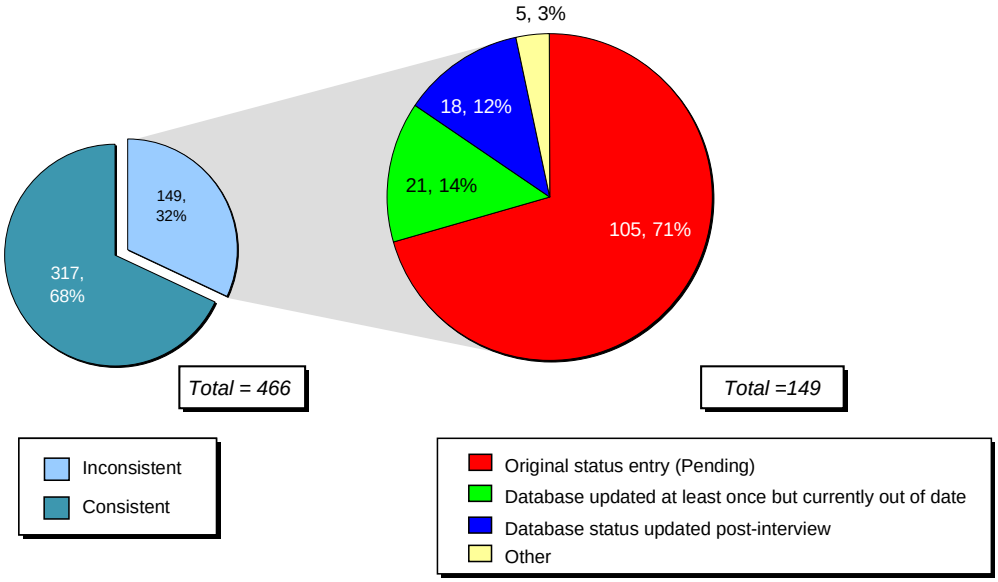
The PMC database relied on verification of information from reviewers to maintain accuracy; however, reviewers were frequently delayed in verifying the PMC status. The status in the PMC database was inconsistent with the status reported in FDA interviews for 32 percent of the PMCs (Exhibit 21). Twelve percent of this discrepancy was due to a status change after the interview. But 85 percent of these inconsistencies were PMCs for which updates had not been validated in a timely fashion, including 71% for which no status update had ever been delivered[27] by the review staff for entry into the PMC database[28]. Concerns over inaccurate status reporting on the public PMC website was one of the most frequent comments during sponsor interviews.

[26] There is no guidance or regulation that requires FDA to follow up on PMCs that have missed milestones.

[27] The 71% figure includes both products for which no annual status report had been received from industry and products for which FDA review staff had never validated an annual status report that was submitted.

[28] PMC status was gathered from the PMC database at least twice over the course of the study, in July and December 2006. The 32 percent discrepancy noted represented an approximately 50 percent improvement in PMC status accuracy from the beginning of this study, suggesting that interaction with RPMs and reviewers regarding the status led to an increased timeliness and accuracy in status verification.

Exhibit 21: Consistency in PMC Status Between FDA Databases and Interviews



Sources: FDA Interviews and tracking databases

FDA did not typically contact sponsors regarding delayed PMCs except in rare cases; in those cases the following triggers were cited:

- Review of the annual status report
- Discussion of outstanding PMCs during monthly/quarterly administrative rounds (mentioned by one division)
- Personal interest in the product or study by an individual reviewer (very rare).

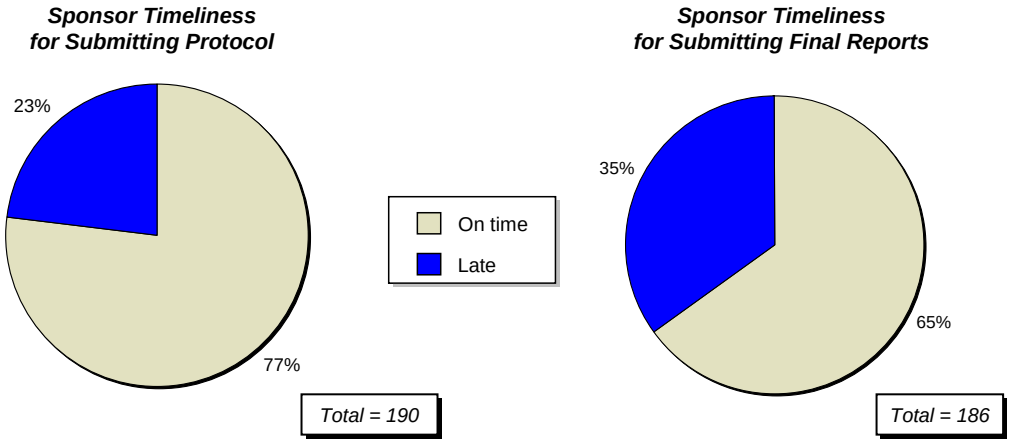
4.4.4 Timeliness of Sponsor Submission and FDA Review

The timeliness of sponsor submissions of protocols and final study reports was determined by comparing the action letter goal dates with actual submission dates. Sponsors were late in submitting protocols nearly one-quarter of the time and late in submitting final study reports more than one-third of the time[29] (Exhibit 22). During interviews, several sponsors noted that delays in receiving feedback from the FDA on protocol submissions had forced them to either conduct the study at risk in order to stay on schedule or to fall behind schedule while awaiting protocol approval or feedback.

In cases where FDA and sponsor agreed to a renegotiated timeline, FDA regulations required the PMC status to reflect the original milestone dates rather than the newly established ones. This led to the appearance of delayed studies that were actually proceeding according to a revised agreed-upon schedule.

[29] For the purpose of this analysis, sponsor submissions were considered late if they were received more than one month after the due date specified in the action letter.

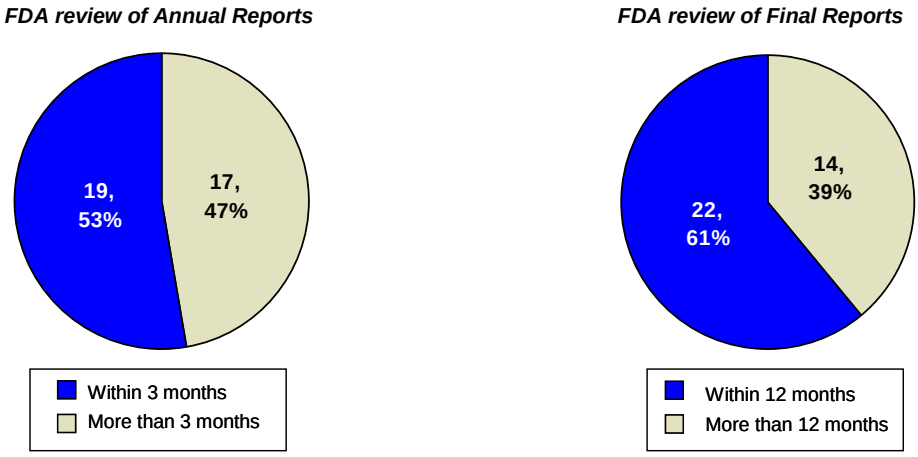
Exhibit 22: Timeliness of Sponsor PMC Submissions



Sources: FDA Interviews and tracking databases

The FDA's three-month goal for review of annual status reports was missed 47 percent of the time, while the 12-month goal for review of final study reports was missed 39 percent of the time[30] (Exhibit 23). In both cases, the primary reason given for missed deadlines was heavy reviewer workload and that PMC review-related tasks were often given a lower prioritization as compared to application review. FDA reviewers also cited the inability to impact outcomes, primarily because there were no penalties for sponsor non-compliance, factored into the low prioritization of PMC submission reviews. Also, during the data gathering phase of this study it was notable that changes in FDA staff, particularly the regulatory project manager or medical officer, negatively impacted the level of knowledge of and responsibility for PMC tracking and review.

Exhibit 23: Timeliness of FDA Review of PMC Submissions



Source: FDA Interviews

[30] The review timeframes for annual status reports and final study reports are described in 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 (February 2006).

4.4.5 Best Practices Observed

Best practices observed in tracking and reviewing:

- Review outstanding PMC status during monthly or quarterly rounds
- Assign a PMC gatekeeper for the division, to track status and contact sponsors
- Maintain matrix of PMC milestone dates
- Hold transition meetings to facilitate knowledge transfer when staff turnover occurs

Certain review divisions/offices had developed practices and processes to promote more accurate tracking and timely review, which could be adopted broadly. For example, some divisions/offices reviewed outstanding PMCs during monthly or quarterly rounds and encouraged reviewers to verify the status or contact sponsors for PMCs that had passed a milestone date without a submission. Another practice was to assign a "PMC gatekeeper" for the division, who was responsible for tracking status and contacting sponsors.

At the RPM level, effective practices included maintaining a matrix of all PMC activity and submission dates (updated monthly) and regularly verifying the status as reported in the PMC section of the annual report. At least one division had held transition meetings when a RPM left the position and provided the new RPM with a complete history and status update for all PMCs associated with the products being transferred to the new RPM. This transition ensured an effective handoff of responsibility for PMC review when staff turnover took place.

4.5 Public Health Impact

The role of PMCs in the drug development process is to increase safety, efficacy and optimal use of a product after it has been approved for marketing and is available to patients. While a single, clear metric through which to gauge the public health impact of PMCs was difficult to ascertain, several proxy measures were developed. First, a public health benefit was assumed for any PMC that resulted in a label change, since the PMC yielded information that directly impacted the way a product was prescribed and used. Yet this definition alone was too narrow, since studies that did not lead to a label change could contribute to public health by expanding the safety profile, optimizing usage of a product, or satisfying/confirming concerns that initially led to the study. During interviews, FDA reviewers characterized the outcomes of fulfilled postmarketing studies associated with their products and provided a specific description of the public health benefit for each fulfilled study[31]. Sponsor perceptions of the value to public health of conducting PMCs were also ascertained through interviews.

Fulfilled postmarketing studies resulted in a label change just over half (51 percent) of the time (Exhibit 24). The most common study outcomes were:

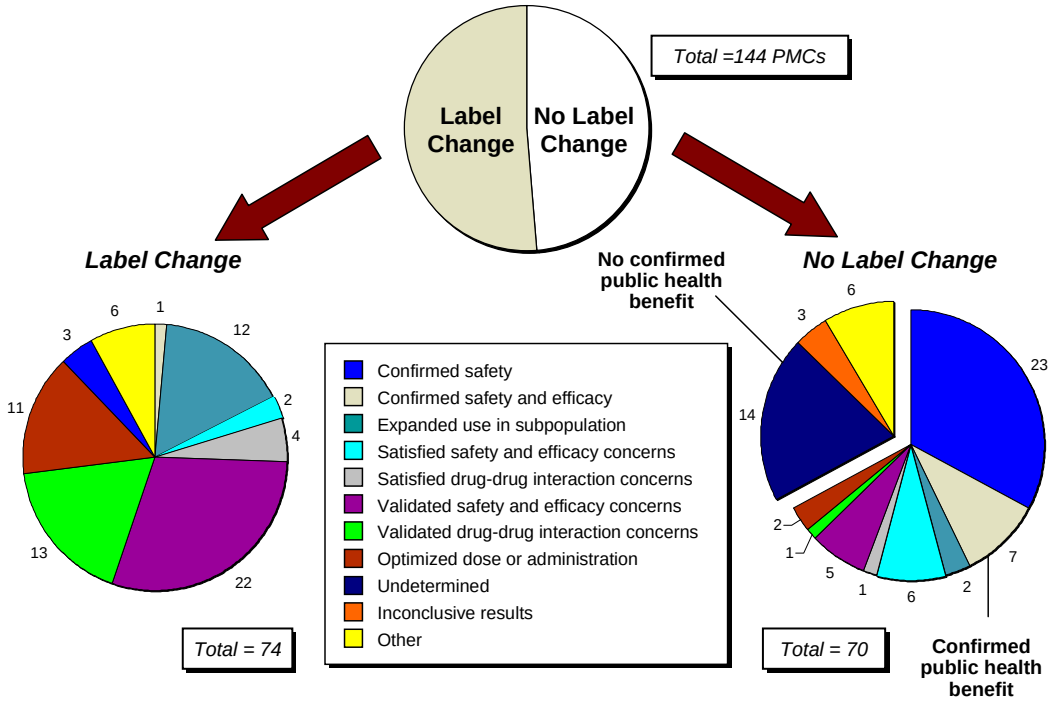
- Validated safety and efficacy concerns
- Optimized dose or administration
- Expanded use in a subpopulation
- Validated drug-drug interaction concerns.

For those studies that did not yield a label change, more than two-thirds still had a confirmed public health benefit, with the most common outcomes being:

- Confirmed safety
- Confirmed safety and efficacy
- Validated safety concerns.

[31] Interviews covering 144 of the cohort's 224 fulfilled PMCs were used to verify label change and ascertain public health benefit.

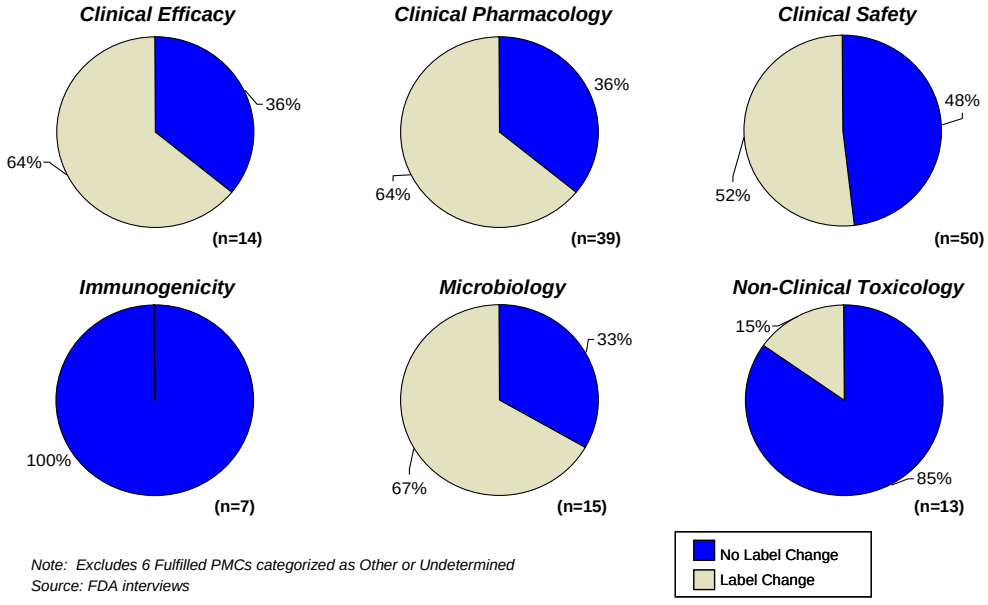
Exhibit 24: Fulfilled PMC Impact on Label Changes



Note: Excludes 80 Fulfilled PMCs for which the presence of a label change was not determined

The likelihood of a fulfilled study resulting in a label change varied, depending on the type of study. Microbiology, clinical efficacy and clinical pharmacology studies were the most likely to result in label changes, while immunogenicity and non-clinical toxicology PMC studies rarely did (Exhibit 25). One reason for the lack of label changes for immunogenicity studies is that many of these PMCs were for assay development to support a clinical trial in a separate postmarketing study, rather than an actual study relating to the product.

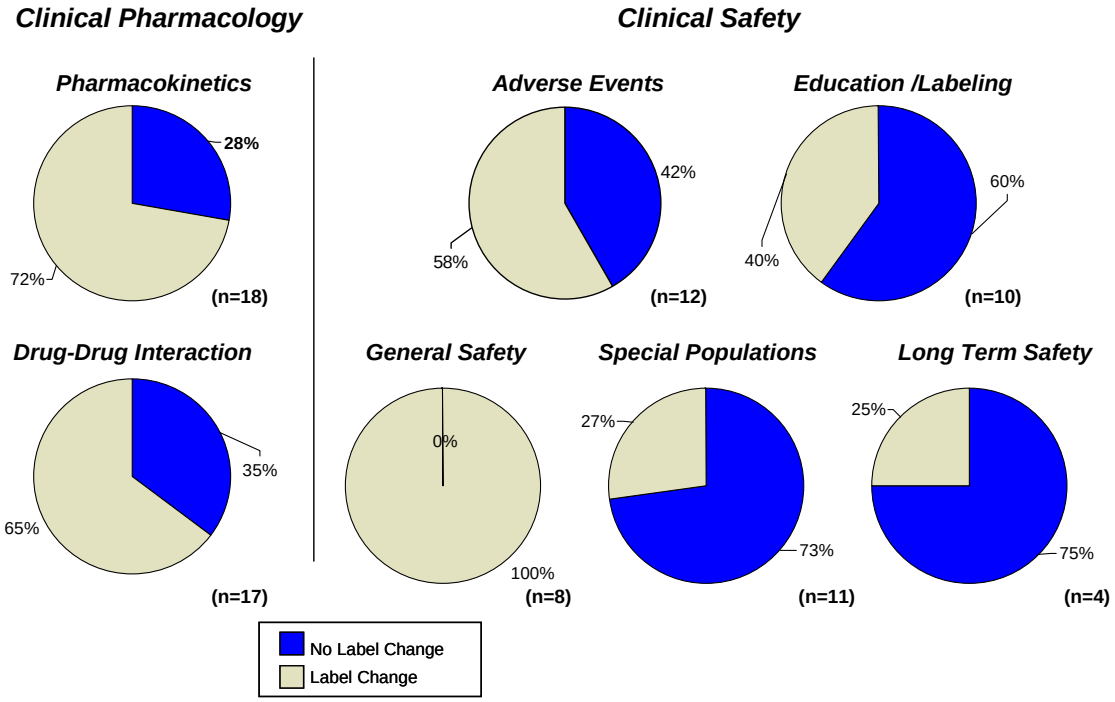
Exhibit 25: Label Changes by PMC Study Category



Note: Excludes 6 Fulfilled PMCs categorized as Other or Undetermined
Source: FDA interviews

Within each study type, certain study subcategories were more likely to result in label changes. Both pharmacokinetic and drug-drug interaction studies (subcategories of clinical pharmacology PMCs) resulted in label changes approximately three-quarters of the time (Exhibit 26). Within clinical safety PMCs, some study subcategories were likely to result in label changes, such as general safety and adverse events, while others such as special populations and long-term safety studies were not.

Exhibit 26: Label Changes by Study Subcategory



Source: FDA interviews

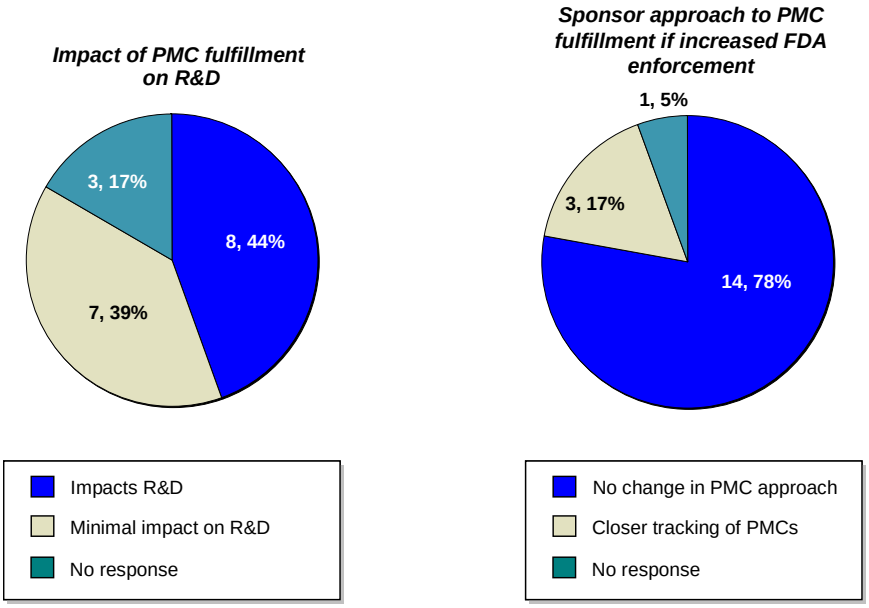
The observed public health benefit of PMCs was corroborated by sponsors with products in the study cohort that completed a customer satisfaction survey. Eighty-six percent of respondents agreed that PMCs enhance public health by addressing concerns about or improving the safety, efficacy or optimal use of the product. In particular, sponsors believed that studies that resulted in a label change were beneficial to the public health, because new information on safety or optimal use was made available. However, half of the interviewed sponsors indicated that in their experience, the rationale for some PMCs was unclear and had questionable public health benefit. For example, sponsors noted that some studies were already underway or would have to be conducted even in the absence of the PMC (e.g., adverse events reporting), so the commitment did not yield any data that FDA would not have received without a PMC. Some sponsors also said that some PMCs appeared to be designed to satisfy an academic interest, rather than a public health concern.[32]

[32] An example, cited by one sponsor, of a PMC believed to satisfy a reviewer's academic interest was an additional clinical pharmacology study that the sponsor did not feel added to the product's safety or efficacy profile or enhanced optimal use.

Sponsors' internal approaches to funding PMC completion varied; half of the sponsors surveyed allocated separate resource pools for conducting new product and PMC research (Exhibit 27). Sponsors had divided opinions on the impact of completing PMCs on new drug research and development. Half of the sponsors who responded to the survey said that conducting PMCs does not significantly impact other R&D activities, because they considered PMCs to be important activities for maintaining marketed products, rather than an alternative to other R&D. Those sponsors who said it did impact R&D noted having limited resources and that any research activity necessarily impacted the amount of R&D for new products.

Virtually all sponsors indicated that PMC execution was a high priority and felt a strong sense of commitment to honor any agreement with FDA. Most sponsors indicated that maintaining an on-time PMC status was important both to their company and to the physicians, patients, and patient advocacy groups that used or influenced use of the product. Since the public PMC database was the primary tool used to display PMC status, most sponsors actively reviewed the PMC website and were concerned when the information was inaccurate. Almost all of sponsors claimed that additional FDA enforcement options would not impact their approach to conducting studies because PMCs were already a significant priority.

Exhibit 27: Sponsor Perspectives on R&D Impact of Conducting PMCs and Potential Enforcement Options



Source: Sponsor interviews

5. RECOMMENDATIONS

The recommendations developed in this analysis for PMC development, rationale, tracking and review are detailed below.

5.1 PMC Development and Rationale Recommendations

The main areas for improvement in the PMC development process are:

- Communicate the review gap and proposed PMC to the sponsor earlier in the review process
- Increase transparency of decision-making process through documentation, which will likely improve consistency and reduce inter-divisional/office/center differences in decision-making processes.

FDA should make efforts to notify sponsors of issues that could lead to PMCs earlier in the review process. This could be achieved through informal communication after the preliminary discipline review is conducted, but before it is finalized. Notification would not guarantee that a PMC request was forthcoming, but rather grant the sponsor additional time to understand the concern, develop a feasible study to propose, or provide evidence demonstrating that the study is not necessary. Providing earlier notification would likely result in fewer PMCs and better study design for those that are ultimately agreed upon.

The GRMPs recommendations contain several PMC-related milestones, including negotiation of PMCs, if needed, in the action phase. This milestone is to occur three weeks before division sign-off of the application, but many sponsors indicated that they had much less time than this to evaluate certain PMCs. FDA should include training on these GRMPs milestones to ensure that reviewers are aware of them. Encouraging adherence to the GRMPs recommendations would ensure the opportunity for sponsor evaluation and thoughtful PMC discussion of study rationale and design, which should improve sponsor compliance and study outcome. FDA may need to determine if additional resources are required to train staff and fully adopt the GRMPs.

The process of developing PMCs does not lend itself to an inflexible decision tree process, but more rigor in the process of developing the PMC would help weed out “nice to know” agreements and result in greater consistency in PMC requests across divisions/offices. This process may be facilitated by a PMC development template, which would be developed by FDA and integrated into FDA’s quality systems processes. As part of a larger quality systems initiative for PMCs, the process template would be monitored and revised over time to include additional FDA needs, reflect FDA experience with PMC types, and potentially provide additional guidance to industry on FDA’s expectations of clinical evidence to be submitted in certain applications.

In the sample template (Exhibit 28), the first two questions require FDA to characterize the issue or data gap and the reason for post-approval timing. The choices listed were designed, in part, to eliminate vague or questionable PMC rationales. This problem would also be mitigated by ensuring that the rationale is documented in the discipline review template, which would also allow for a more thorough and descriptive explanation of the rationale for the study and timing. The third question was designed to ensure that there has been sufficient discussion and opportunity for clarification of the issue and proposed studies with the sponsor. Implementing the GRMPs milestone for PMC discussions and making efforts to notify sponsors of potential PMC issues earlier in the review should allow for these questions to be answered affirmatively. The discipline review team lead would be asked to commit the necessary resources for tracking and review of the commitment, a best practice observed in some divisions/offices to promote a more selective use of PMCs to resolve important issues.

Exhibit 28: Sample PMC Development Template

- Characterize the review gap leading to this PMC.
  - ❑ Required by regulation (e.g., accelerated approval or animal efficacy confirmatory studies; or pediatric study requirement)
  - ❑ Additional data/analysis requested for a submitted/expected study (Provide explanation)
  - ❑ Potential safety signal in submitted studies
  - ❑ Subpopulation studies needed
  - ❑ Drug-drug interaction concerns
  - ❑ Additional dosing studies needed
  - ❑ Long-term study
  - ❑ Other (Provide explanation)
- Explain why this issue is appropriate for a PMC instead of a pre-approval requirement (e.g., Unmet need, life threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation impacted, theoretical concern).
- Is the PMC clear and feasible?
  - ❑ Are goal dates and expectations clear?
  - ❑ Has the sponsor had sufficient time to review the PMCs, ask questions, and determine feasibility?

Review Team Leader or Supervisor/PMC Development Coordinator: Acceptance of this PMC indicates it has sufficient value to public health to commit necessary staff for timely tracking and review

5.2 PMC Tracking and Review Recommendations

In general, a gap was observed between the level of effort required to accurately track and review PMCs and the priority placed on these tasks by FDA relative to other reviewer and RPM tasks. This gap should be reconciled by either a more selective use of PMCs, which would decrease the overall workload, or an increase in priority and incentive for accurate tracking and review. Monitoring the frequency of status updates and prompting non-responsive teams to submit status updates would also increase the PMC database accuracy. Providing training on PMC tracking processes and responsibilities for new RPMs and reviewers would likely improve compliance with status updates and accuracy. FDA would need to determine if additional resources are required to implement this recommendation.

FDA should reflect renegotiated timelines in their internal databases and PMC website when tracking and reporting the current status of PMCs. In many instances, new PMC schedules had been renegotiated and agreed upon by both sponsor and FDA, because the original schedule proved to be infeasible for reasons unrelated to the sponsor's level of effort to conduct the study. However, as required by regulations, these commitments were reported as delayed if they missed any milestone date in the original study schedule. This practice negatively impacts the perception of timeliness of the PMC pool by combining studies currently underway using a revised, agreed-upon timeline with those studies that are truly delayed. For situations where delays occurred due to circumstances beyond the control of the sponsor, a possible option for FDA to consider is to release and reissue commitments where FDA and the sponsor agree that the original study schedule cannot be met and a revised schedule is needed.

Exhibit 29 summarizes suggested process improvement opportunities identified in the PMC analysis, organized by general timeframe for implementation. To implement these short-term and long-term improvement opportunities, FDA should assess the need for additional resources.

- *Short-Term Opportunities*: Cross-divisional expansion of already existing best practices and limited modification to existing procedures.
- *Long-Term Opportunities*: Significant change to existing processes or establishing new procedural milestones.

Exhibit 29: Summary of PMC Recommendations

	Short-Term	Long-Term
PMC Development	• Whenever possible, notify sponsors of issues that may lead to PMCs early in the review, to allow time for development of a workable approach or to supply evidence showing the PMC is unnecessary	• Emphasize PMC-related GRMPs milestones in PMC training to allow for earlier notification and feasibility and study design discussions
PMC Rationale	• Assign a division-level PMC gatekeeper to review all PMCs before they are requested to ensure consistency • Ensure sufficient resources are available to monitor PMC progress and review submissions before requesting the PMC • Limit PMC requests to studies with defined end points • Clearly document PMC rationale in the Clinical review template	• Adopt a clear PMC definition and a cross-divisional worksheet to ensure consistent rationale and quality when developing PMCs • Implement a quality system to control and improve PMC quality and consistency across divisions/offices
PMC Tracking and Review	• Assign a PMC gatekeeper to check the status of PMCs and follow up with all sponsors on status • Verify the status of annual and final report submissions on a periodic basis to determine if any are delayed • Hold transition meetings to transfer PMC information to new RPM/ reviewer when staff change • Consistently update revised study schedules in the internal PMC databases	• Create automatic reminders/alerts to remind non-responsive teams to submit updates, including any renegotiated PMC schedules • Adopt a quality systems process to ensure PMC responsibilities are met and document monitoring occurs • Provide training on the PMC tracking policy to ensure RPMs and reviewers understand expectations • Display renegotiated timelines on the PMC website • Consider releasing PMCs with schedules that have been renegotiated, and create new PMCs with the revised milestone dates