Food and Drug Administration

Independent Evaluation of FDA's Prescription Drug User Fee Act – Evaluations and Initiatives; CDER Technical Support and Analysis

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Deliverable 2-8:
Final Report on the PMR/PMC Backlog Review

April 10, 2009

Booz | Allen | Hamilton

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1. EXECUTIVE SUMMARY

In addition to the oversight requirements afforded to the Food and Drug Administration (FDA) under Section 506B of the Federal Food, Drug and Cosmetic Act (FDCA),[1] the Food and Drug Administration Amendments Act of 2007 (FDAAA) expanded the authority to require sponsors to conduct and report on postmarketing studies and clinical trials. A postmarketing requirement (PMR) is a study or trial that a sponsor is required by statute or regulation to conduct post-approval. A postmarketing commitment (PMC) is a study or trial that a sponsor agrees in writing, but is not required by law, to conduct post-approval. PMCs and FDAAA PMRs are typically derived from a gap in product information that FDA identifies in an application, but has determined through a carefully deliberated process that resolving the information gap is not a condition of approval.

Section 506B of the FDCA requires FDA to track and monitor the progress of PMRs and PMCs to ensure that they are completed in a timely manner. FDA accomplishes this task primarily by reviewing the annual status reports submitted by the sponsor for completeness and accuracy. In recent years, there has been increased scrutiny on both FDA and the pharmaceutical industry regarding the number of PMCs and PMRs categorized as pending, and that therefore appear to have not been initiated.[2] In light of this concern, section 921 of FDAAA added a requirement for FDA to review the entire Backlog of postmarketing study commitments and requirements on an annual basis to determine which commitments should be revised or released. FDA contracted with Booz Allen Hamilton to conduct this Backlog review. The objectives of this task were to:

- Propose recommendations for FDA re-evaluation or closure of PMRs and PMCs
- Identify PMRs and PMCs that need study/trial completion dates
- Analyze commitments that are recommended for closure/re-evaluation to determine why the studies/trials may be no longer necessary or feasible

For the Backlog review, FDA used internal PMR/PMC tracking systems to produce a list of open non-Chemistry, Manufacturing, and Controls (CMC) PMRs and PMCs. The study was based on a cohort of 1531 open PMRs/PMCs as of September 27, 2007, which constituted the PMR/PMC Backlog. Current actual PMR/PMC status was determined based on data gathered from internal FDA systems and documents from the document room archives. Once the accurate statuses were determined, the Backlog PMRs/PMCs were prioritized for detailed review based on a previously developed prioritization scheme and used to develop recommendations. Recommendations were validated by review division advisory groups and tracking coordinators, who accepted or revised the recommendations.

Status Updates

Determining the accurate current status for PMRs/PMCs in the Backlog was essential because the prioritization scheme that determined how PMRs/PMCs were reviewed for potential release or revision was dependent on the PMR/PMC status.[3] PMRs/PMCs in the Backlog were selected for a status update review if they met one of two criteria: their current status in the database was inconsistent with the study/trial schedule milestones or the PMC was categorized

[1] PMCs are detailed in the Food and Drug Administration Modernization Act of 1997 (FDAMA), which became law on November 21, 1997. Section 130(a) of Title I of FDAMA added a new provision (section 506B) on postmarketing studies to the Federal Food, Drug, and Cosmetic Act 356b (21 U.S.C. 356b).

[2] For example, see "Industry Reneges on Postmarketing Trial Commitments", Nature Biotechnology, Vol. 21, No. 7, Bouchie, A. (2003) and Conspiracy of Silence: How the FDA Allows Drug Companies to Abuse the Accelerated Approval Process", (2005)

[3] Status definitions are characterized by regulation 21 CFR 314.81.

as pending in the database and either had no milestone dates or only a final report submission date in its study/trial schedule. Overall, 93% of the Backlog PMRs/PMCs were reviewed for status update or verification either based on these criteria or because an annual status report was received and reviewed during the course of the task. Of those PMRs/PMCs reviewed, the status listed in the PMC database was verified as accurate for 42% of the PMRs/PMCs and was inaccurate and required an update for 51% of the PMRs/PMCs. Status updates to the PMR/PMC database are typically made through one of three ways: completing and archiving annual status report summaries, notifying the PMR/PMC database manager of submissions received, and issuing properly-coded letters of fulfillment or release to sponsors. The most common explanation for an inaccurate status in the PMR/PMC database was PMR/PMC Annual Status Reports (ASRs) not reviewed or the corresponding annual status report summary not archived (47%) in FDA data systems (for NDAs) or sent to the PMR/PMC database manager (for BLAs) . Regulatory Project Managers (RPMs) who were unaware of final report submissions (44%) and lack of updates when study/trial start or finish milestones pass (9%) were the other contributing factors to errors in the database.

The distribution of Backlog PMR/PMC statuses changed significantly between September 27, 2007 and the end of this review. On the date FDAAA was enacted, 63% of Backlog PMRs/PMCs were categorized as pending, 15% ongoing, 14% submitted, and 7% delayed. After reviewing and updating the PMR/PMC status, the largest segment of Backlog PMRs/PMCs are accurately categorized as submitted (36%), followed by delayed (15%), ongoing (14%) and pending (14%). Previously it appeared that most studies/trials had not yet been initiated, leading to public criticism of both FDA and the pharmaceutical and biotech industry for not conducting their studies/trials. However, the updated status data show that most PMRs/PMCs have been initiated and more than half of them were either submitted, fulfilled or released. The largest segment of PMRs/PMCs is now awaiting FDA review of a sponsor-submitted final report.

Recommendations: Standardize sponsor annual status report submissions and streamline FDA annual status report reviews by creating an interactive form that requires sponsors to enter all necessary data. Accurately process fulfill and release letters, creating multiple letters if necessary, to ensure that the status is updated when a PMR/PMC is closed.

Off-Schedule PMCs and PMRs

PMRs/PMCs can be classified as either on-schedule or off-schedule, depending on their status category. Sponsors with on-schedule PMRs/PMCs are making progress toward completing the study or trial according to their assigned schedule, and the status of those PMRs/PMCs is pending, ongoing or submitted. Off-schedule PMRs/PMCs are those that are not currently progressing according to the original study/trial schedule, and are therefore classified as either delayed or terminated. Sponsors missing the agreed-upon deadline for submission of the final report was the cause of 87% of delayed PMRs/PMCs, while only 3% were delayed in completion of the study/trial. This large disparity is likely explained by the fact that only 14% of PMRs/PMCs have a study/trial completion milestone date, while 70% have a final report milestone date. Further, FDA does not require any regulatory correspondence from sponsors to notify FDA that a study/trial has started or completed, making it difficult to determine whether a PMR/PMC has missed a study/trial start or completion date.

Off-schedule PMCs were present in noticeable proportions across most review divisions/offices. Divisions with the most off-schedule PMCs were the Divisions of Biologic Oncology Products (DBOP), Anti-Viral Products (DAVP) and Drug Oncology Products (DDOP). The difference by division could partially be explained by the fact that certain divisions have different policies for handling off-schedule PMCs.

Recommendations: Write PMRs/PMCs to meet specific objectives rather than specific protocols or studies, so that if the original study/ trial proves infeasible, there is still flexibility to fulfill the commitment with another study/trial. FDA should notify sponsors with a standard template response that they may not provide feedback for a protocol submission so sponsors may initiate their studies/trials and not fall off schedule while awaiting protocol feedback that FDA may determine is unnecessary. Otherwise, FDA should establish a Center-wide policy for timely review and feedback for sponsor protocols. FDA is now able to enforce compliance with study/trial schedules for PMRs created under FDAAA, and should issue Dunner letters when sponsors miss a final study/trial report date to remind and encourage them to complete their non-FDAAA PMRs/PMCs on time.

Submitted PMRs/PMCs

Tracking and review is an important part of the PMR/PMC process, ensuring successful and timely completion of these commitments. For each PMR/PMC, FDA and sponsors usually agree upon significant milestone dates for study/trial completion and final report submission. For PMRs/PMCs that are clinical studies or trials, typical milestones include: protocol submission, study/trial start, study/trial completion and final report submission. The current status of a PMR/PMC is characterized by the progress made by the sponsor against the original study/trial schedule and milestone dates. A PMR/PMC is classified as submitted once FDA receives the final study/trial report. Analysis of the status changes for this task indicates that the majority of PMRs/PMCs with status changes were updated to submitted.

FDA's internal goal for completing review of PMR/PMC final report submissions is 12 months. In this task, FDA met its goal of timely review of final reports only 23% of the time, whereas final reports for 77% of the PMCs classified as submitted were received more than 12 months ago. The main reasons for failure to meet review goal dates were competing workload priorities and lack of available review staff.

Recommendations: Ensure that updates to the PMR/PMC database occur when final report submissions are received. FDA should proactively facilitate the timely review of submitted study/trial reports.

PMRs/PMCs Lacking Final Report Milestone Dates

When establishing PMRs/PMCs, FDA typically collaborates with sponsors to determine specific milestone dates that are subsequently used during the PMR/PMC lifecycle to track progress and determine status. When a sponsor completes a study/trial and submits a final report, the appropriate review division will assess whether the report satisfies the PMR/PMC. Once FDA

has reviewed the report and notified the sponsor that the PMR/PMC has been satisfied, the PMR/PMC is categorized as fulfilled and removed from the Backlog. Of the Backlog PMRs/PMCs, there were 458 (30%) that had no specific completion date associated with them, which led to the categorization of a significant number of commitments remaining indefinitely in a pending or ongoing status category. Although the greatest number of PMRs/PMCs in the Backlog were created in the last four years, nearly half (46%) of the PMRs/PMCs without completion dates were created more than 10 years ago. This finding suggests that FDA has improved its practices based on experience and wider adoption of PMR/PMC development policies.

Recommendations: Establish specific study/trial start and final report submission milestone dates. FDA should consider creating a new mechanism to allow sponsors to notify FDA of study/trial initiation. This new reporting strategy would allow sponsors and FDA to streamline the reporting process and improve the accuracy and compliance of PMR/PMC status updates. FDA should record the actual dates of study/trial milestone progress and completion in the PMR/PMC databases to facilitate tracking with relative milestone dates.

Backlog PMR/PMC Recommendations

The main objective of the Backlog review was to identify PMCs for possible re-evaluation or closure (i.e., release or fulfill). Of the 1531 PMRs/PMCs in the Backlog, 81% were issued recommendations through a prioritization scheme based on the PMR/PMC status and the presence or absence of a final report submission milestone. Recommendations were not issued to PMRs/PMCs that were closed (i.e., fulfilled or released) or when the correct status was undetermined. For the purpose of priority determination, open PMRs/PMCs were categorized into three groups: off-schedule (20%), on-schedule with no final report submission date (12%), and on-schedule with a final report submission date (68%). Booz Allen recommended no change for 81% of the PMRs/PMCs in the off-schedule category. Of the on-schedule PMRs/PMCs with no final report submission dates, 73% were issued a recommendation to establish completion dates since the sponsor had not reported on the status within the last two years. PMRs/PMCs identified for re-evaluation included 40% off-schedule PMRs/PMCs, 59% on-schedule PMRs/PMCs with no final report submission date, and 1% on-schedule PMRs/PMCs with a final report submission date. For the off-schedule PMRs/PMCs, 43% were recommended for release. Most of the PMRs/PMCs (60%) recommended for fulfill had been reviewed by FDA staff who had internally documented that the PMR/PMC should be fulfilled. The age of a PMR/PMC did not appear to be a significant factor for those PMRs/PMCs recommended for release. Most of the PMRs/PMCs recommended for re-evaluation and release were in the Division of Medical Imaging and Hematology Products (DMIHP) and the Division of Special Pathogen and Transplant Products(DSPTP). The majority (59%) of PMRs/PMCs recommended for re-evaluation did not have final report submission dates and 34% of the release recommendations were issued because the product was withdrawn from the market.

2. TASK BACKGROUND, OBJECTIVES AND SCOPE

Postmarketing requirements (PMRs) and postmarketing commitments (PMCs) are studies or trials that are conducted by a sponsor after FDA has approved a product for marketing. Although these products have been determined as safe and effective for marketing, these studies/trials are intended to further define the safety, efficacy, or optimal use of a product or to ensure consistency and reliability of product quality (i.e., CMC commitments), and therefore play a vital role in fully characterizing the product.

A PMR is a study or trial that a sponsor is required by statute or regulation to conduct post-approval. The circumstances under which FDA may require a sponsor to conduct a study or trial include:

- Confirmatory trials to demonstrate the clinical benefit of a product following Accelerated Approval (21 CFR 314.510 and 601.41)
- Pediatric studies for products not adequately labeled for children, required as part of the Pediatric Research Equity Act (PREA; 21 CFR 14.55(b))
- Studies needed to confirm safety and efficacy in human subjects for products approved under the Animal Rule (21 CFR 314.610 (b)(1) and 601.91(b)(1))
- Studies to assess a known serious risk, assess signals of serious risk, or identify an unexpected serious risk related to the use of a drug (Food and Drug Administration Amendments Act of 2007 (FDAAA), Title IX, Section 901)[4,5]

A PMC is a study or trial that a sponsor agrees in writing to conduct after approval of the product. PMCs are typically derived from a gap in product information that FDA identifies in an application, but has determined through a carefully deliberated process that resolving the information gap is not a condition of approval.

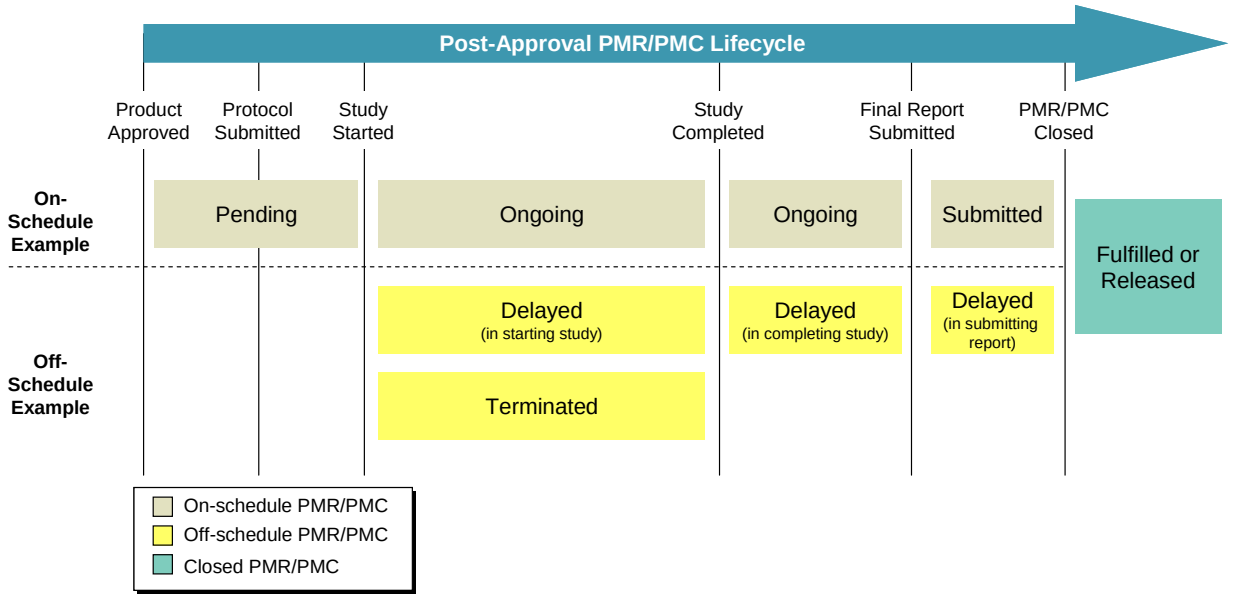
Each PMR/PMC is classified under one of the seven status categories[6] (pending, ongoing, submitted, delayed, terminated, fulfilled, and released) that define the progress of the study or trial throughout the PMR/PMC lifecycle in relation to the milestones specified when the PMR/PMC was created (Exhibit 1). Open PMRs/PMCs (i.e., those that have not been fulfilled or released) can be considered either “on schedule” or “off schedule” based on their current status categorization. On-schedule PMRs/PMCs (i.e., pending, ongoing or submitted) are currently at a stage in the PMR/PMC lifecycle that is consistent with the milestone dates set out in the original study/trial schedule, while those that are off schedule (i.e., delayed or terminated) have either missed one of their milestone dates or are not progressing.

[4] Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 901, in Title IX of FDAAA, created a new section 505(o)(3) of the FDCA authorizing FDA to require certain studies and clinical trials for prescription drugs and biological products approved under section 505 of the act or section 351 of the Public Health Service Act. Under FDAAA, FDA has been given additional authority to require applicants to conduct and report on postmarketing studies and clinical trials to assess a known serious risk, assess signals of serious risk, or identify an unexpected serious risk related to the use of a drug. This new authority became effective on March 25, 2008. FDA may now take enforcement action against sponsors who fail to conduct studies and clinical trials required under FDAAA, as well as those required under FDA regulations (see sections 505(o)(3), 505(z), and 303(f) of the FDCA, 21 U.S.C. 355(o)(1), 355(z), and 333(f)).

[5] Since the PMR/PMC Backlog only includes PMRs/PMCs that were open prior to FDAAA enactment, there are no FDAAA PMRs in the Backlog.

[6] These status categories were established and defined in 21 CFR 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8).

Exhibit 1. Post-Approval PMR/PMC Lifecycle



Sponsors of approved drugs and biological products that have entered into an agreement to conduct a postmarketing study or trial must report on the status of the PMR/PMC to FDA within 60 days of the anniversary date of approval of the original application until the study or trial is completed or terminated.[7] These annual status reports are to include the following elements:

- Description of the PMR/PMC
- Original timeline for achieving PMR/PMC milestones (i.e., study/trial initiation, study/trial completion, and final report submission)
- A revised timeline for completing the PMR/PMC, if applicable
- Current status of the PMR/PMC (i.e., pending, ongoing, submitted, delayed, terminated)
- Explanation of status

FDA is also required to track and monitor the progress of PMRs and PMCs to ensure they are completed in a timely manner. This is primarily accomplished by review of the annual status reports submitted by the sponsor for completeness and accuracy. FDA maintains continuously-updated internal databases of all PMRs/PMCs and their current status and meets its obligations for public disclosure of information by reporting on the status of PMRs/PMCs in both an annual Federal Register notice and a public website that is updated on a quarterly basis.

In recent years, there has been increased scrutiny on both FDA and the pharmaceutical and biotech industry regarding the number of PMRs/PMCs that are categorized as pending, and therefore appear to have not been initiated.[8] In light of this concern, Section 921 of FDAAA added a requirement for FDA to review the entire Backlog of PMRs/PMCs on an annual basis to determine if any commitments should be revised or released.[9] For the purposes of this task, the

[7] This reporting requirement is specified in section 506B of the Federal Food, Drug, and Cosmetic Act (FDCA; 21 U.S.C. 356b)
[8] For example, see "Industry Reneges on Postmarketing Trial Commitments", Nature Biotechnology, Vol. 21, No. 7, Bouchie, A. (2003) and Conspiracy of Silence: How the FDA Allows Drug Companies to Abuse the Accelerated Approval Process", (2005)
[9] FDAAA Section 921 states that FDA shall "on an annual basis, review the entire Backlog of postmarket safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments."

PMR/PMC Backlog is understood to consist of all open PMRs and PMCs (i.e., those that have not been fulfilled or released) as of the date of FDAAA enactment (September 27, 2007). The new legislation also requires FDA to report to Congress on these recommendations and to assign completion dates for commitments that do not have a complete study/trial schedule.

2.1. Objectives and Scope

The goal of this task was to review all open non-CMC[10] PMRs and PMCs established and tracked by the Center for Drug Evaluation and Research (CDER) as of the date of FDAAA enactment and provide support for FDA implementation of FDAAA Section 921. PMRs/PMCs established and tracked by the Center for Biologics Evaluation and Research (CBER) were not included in this review. Key task objectives were to:

- Propose recommendations for FDA re-evaluation or closure of PMRs and PMCs
- Identify PMRs and PMCs that require study/trial completion dates
- Analyze PMRs/PMCs that are recommended for closure/re-evaluation to determine why the studies/trials may be no longer necessary or feasible

At the outset of this task, FDA provided a list of 1643 open PMRs and PMCs derived from the internal PMR/PMC tracking systems on September 27, 2007. During the course of the review, Booz Allen discovered a number of PMCs that were erroneously included in or excluded from this group. PMRs/PMCs that were inaccurately included were removed for the following reasons:

- The PMR/PMC was a duplicate[11] of another PMR/PMC in the Backlog
- The PMR/PMC had already been released or fulfilled
- The PMR/PMC was created after FDAAA enactment
- The commitment was not a PMC or PMR
- The commitment was a CMC PMC

PMRs/PMCs that were subsequently added to the Backlog had been excluded for one of the following reasons:

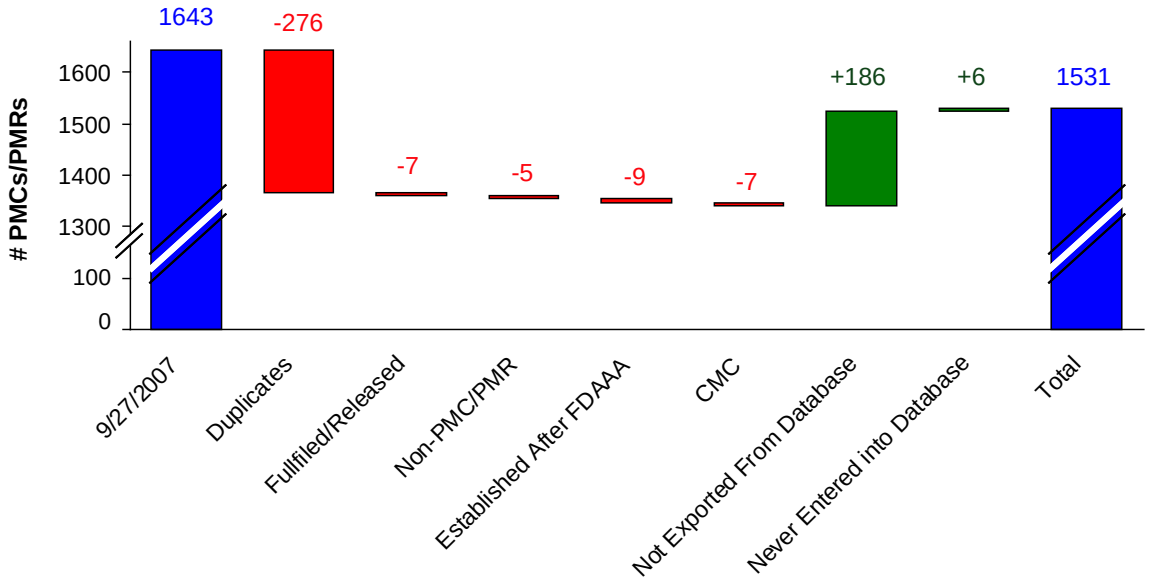
- The PMR/PMC was not exported from the PMR/PMC database when the original list of Backlog PMRs/PMCs was created
- The commitment was never entered into the PMR/PMC database

After accounting for these issues, the actual PMR/PMC Backlog as of September 27, 2007 consisted of 1531 open PMRs/PMCs (Exhibit 2).

[10] CMC PMCs are not required to be tracked under section 506B of FDCA and are not included in the PMC Backlog.

[11] Duplicate PMCs are those that are associated with multiple applications or supplements. In some circumstances, FDA considered multiple applications (i.e., original applications and/or supplemental applications) during the same review and review cycle, issuing a single shared action letter and set of PMCs.

Exhibit 2: **Adjustments to PMR/PMC Backlog Composition**

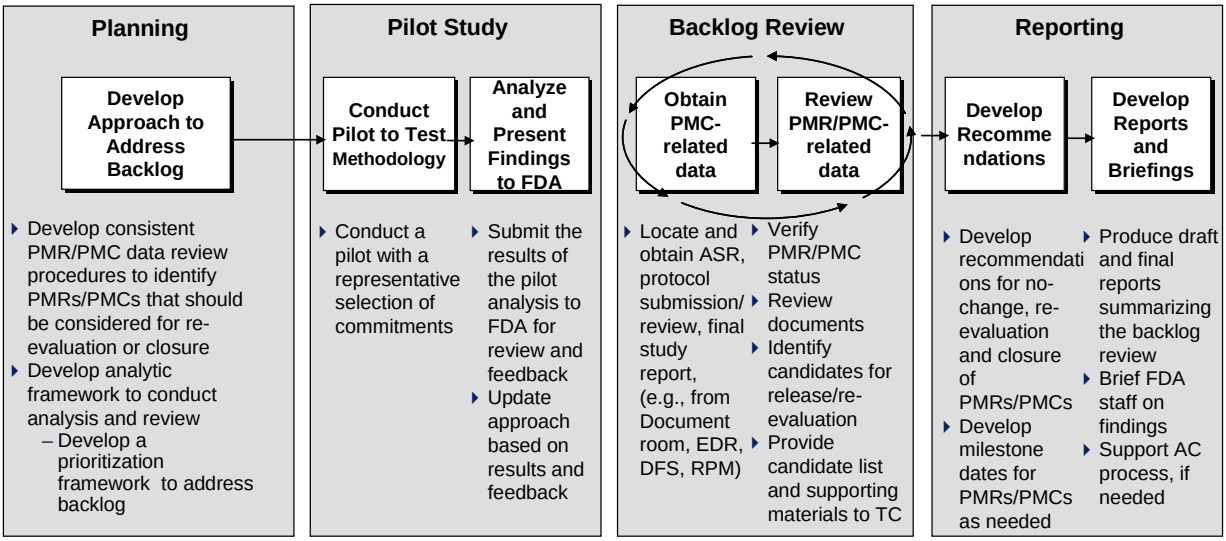


Adjustments to PMC/PMR Backlog Composition

3. METHODOLOGY

The PMR/PMC Backlog review consisted of four phases, shown in Exhibit 3.

Exhibit 3. Technical Approach for Backlog Review



During the planning phase an approach and standard processes for data gathering and review were developed to ensure completeness and consistency during review of the Backlog PMRs/PMCs. A framework was also developed to prioritize Backlog PMRs/PMCs for review for recommendations for closure or re-evaluation, based largely on PMR/PMC status (see Appendix A). A pilot study with ten representative products was then conducted to test and refine the approach and review procedures. Data were gathered from internal FDA systems and documents from the document room archives to determine accurate PMR/PMC status and develop recommendations. After receiving and incorporating FDA input regarding the pilot study, the full Backlog review was initiated by determining the accurate status for all PMRs/PMCs the Backlog, since the prioritization scheme for the Backlog review was dependent on accurate status classification. This was accomplished by first identifying the status of the PMR/PMC listed in the internal PMR/PMC databases and comparing it to the milestone dates established in the product's approval letter. In cases where the milestone dates were inconsistent with the current status in the PMR/PMC database, the correct status was determined by examining documentation, both electronic and paper-based. The types of documents typically reviewed to determine accurate PMR/PMC status included:

- PMR/PMC annual status reports
- PMR/PMC final study/trial reports
- FDA-sponsor communications (e.g., meeting minutes, fulfill letters, release letters)
- Internal FDA memos and reviews (e.g., medical officer review of final study/trial report)

Updated statuses were reviewed by the FDA project technical advisory group (TAG) and the review division before being updated in the PMR/PMC database.

Once the accurate statuses were determined, the Backlog PMRs/PMCs were prioritized for detailed review. Based on the previously-determined prioritization scheme (see Appendix A), certain PMRs/PMCs (i.e., off-schedule PMRs/PMCs and PMRs/PMCs lacking completion dates) were evaluated for potential re-evaluation or release. This was done by conducting a thorough review of all the documentation available for the individual PMR/PMC. Standard approaches for making recommendations were developed and validated by the TAG. Recommendations were reported to the review division's Tracking Coordinators who worked with the review teams to accept or revise the recommendations. PMRs/PMCs lacking completion dates were also identified and reported to the review division to work with the sponsor to establish dates.

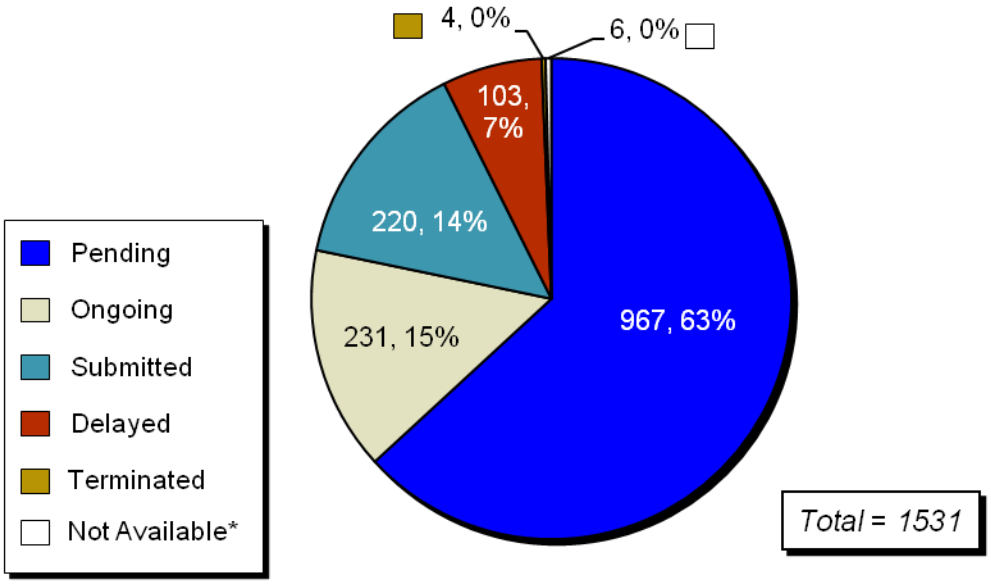
4. FINDINGS

The key findings are presented in the following sections from the PMR/PMC Backlog review. The PMR/PMC Backlog is characterized in the first section. In subsequent sections, findings are presented in accordance with the primary tasks conducted during the study.

4.1. PMR/PMC Backlog Characterization

The cohort defined as the PMR/PMC Backlog that was evaluated for this task included 1233 New Drug Application (NDA) PMRs/PMCs and 298 Biologic License Application (BLA) PMRs/PMCs within CDER that were open as of September 27, 2007. At the beginning of this study, the majority (63%) of the PMRs/PMCs in the Backlog were categorized in the PMR/PMC database as pending (Exhibit 4).

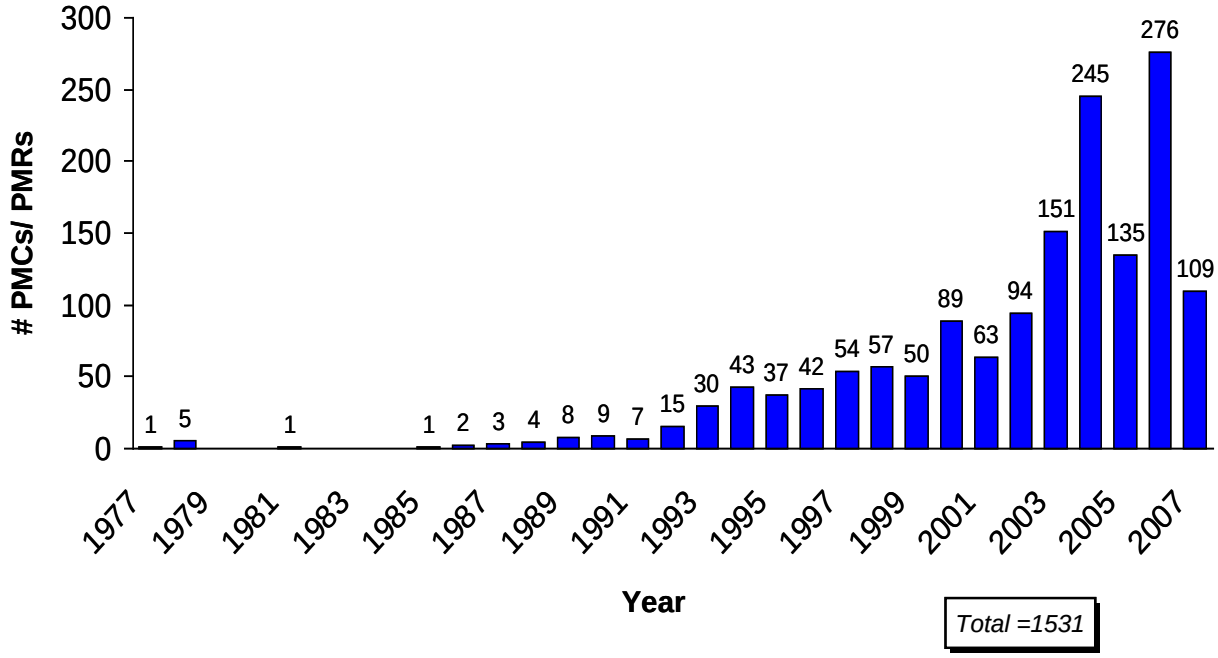
Exhibit 4: PMR/PMC Backlog by Status in Internal PMR/PMC Database as of 9/27/2007



*6 of the 1531 Backlog PMRs/PMCs were incorrectly omitted from the tracking databases as of Sept. 27, 2007

Approximately half (765 of 1531) of the Backlog PMRs/PMCs were created within the last 4 years (Exhibit 5).

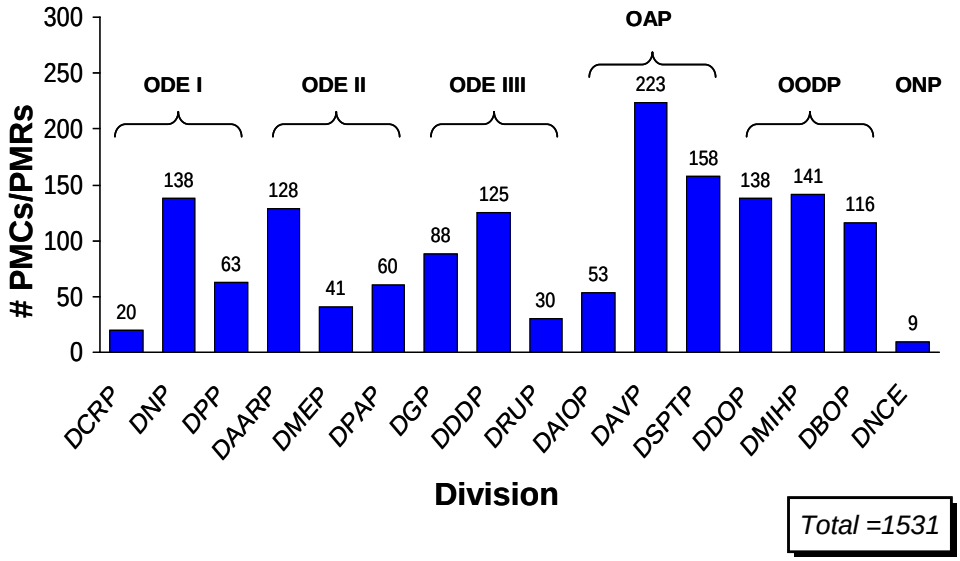
Exhibit 5: PMR/PMC Backlog by Year Established



The number of PMRs/PMCs in the Backlog varied considerably by review division (See Appendix C for Review Division abbreviations). Divisions with the most PMRs/PMCs in the Backlog were the Divisions of Anti-Viral Products (DAVP) and Special Pathogen and Transplant Products (DSPTP) (Exhibit 6). Those with the fewest were the Divisions of Cardiovascular and Renal Products (DCRP), Metabolic and Endocrinology Products (DMEP), Reproductive and Urologic Products (DRUP), and Nonprescription Clinical Evaluation (DNCE). In a prior study, Booz Allen observed that the variation in the number of PMRs/PMCs by review division is consistent with the differences in number of approved products by review division.[12]

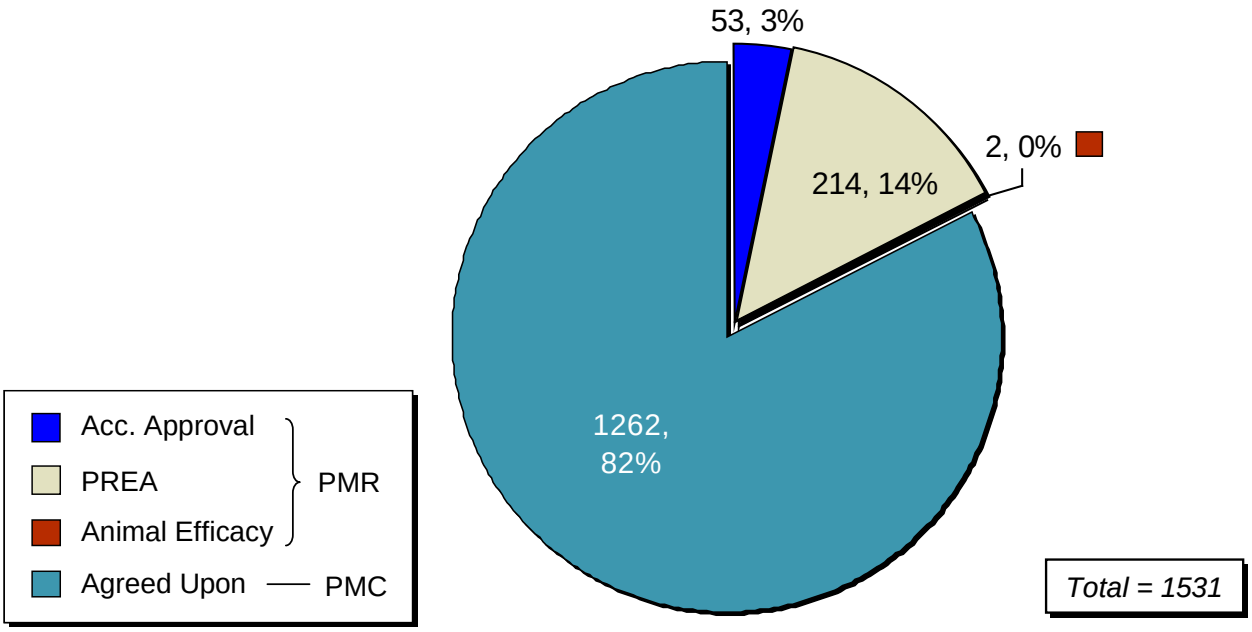
[12] Independent Evaluation of FDA's Prescription Drug User Fee Act III – Evaluations & Initiatives – Postmarketing Commitments Study. Booz Allen Hamilton (January 2008).

Exhibit 6: PMR/PMC Backlog by Review Division



In comparing the distribution of PMR/PMC type, a majority (82%) of the Backlog PMRs/PMCs were PMCs that were agreed upon between the FDA and sponsor and not mandated by legislation. Only 3% of the PMRs/PMCs in the Backlog were established under the Accelerated Approval provision (Exhibit 7).

Exhibit 7: PMR/PMC Backlog by Type



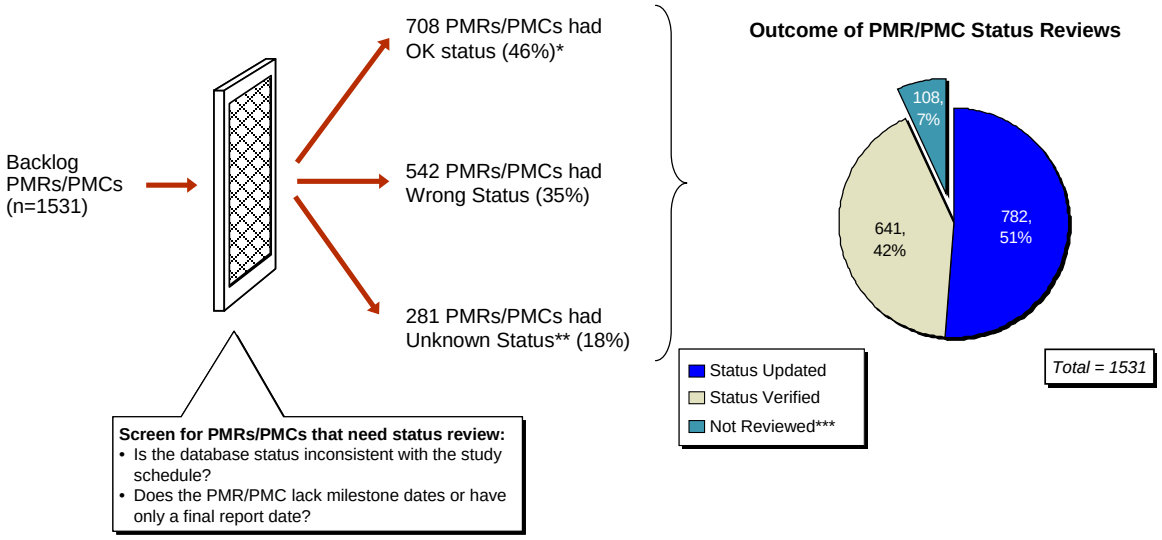
4.2. Status Updates

Out of the 1531 PMRs/PMCs included in this study, 708 (46%) PMRs/PMCs did not require a status review as described in the procedure and approach for PMR/PMC backlog review (see Appendix A) because they had established study/trial milestone dates and the status in the

PMC database was consistent with these milestones (Exhibit 8). Due to inconsistency with the study/trial milestones, 542 (35%) PMRs/PMCs required a status update as of the data lock date of this final report. An additional 281 (18%) PMRs/PMCs were targeted for status review because there were either no milestone dates or they only had a final report submission date and the status had never been updated from pending.

Even though 46% of the Backlog PMRs/PMCs did not require a status review during the course of the study, 1423 (93%) were reviewed for status update or verification based on the criteria discussed in Appendix A or because an annual status report was received and reviewed. Of those PMRs/PMCs reviewed, the status listed in the PMC database was verified as accurate for 641 (42%) PMRs/PMCs. The status was inaccurate and required an update for 782 (51%) PMRs/PMCs. The remaining PMRs/PMCs were not reviewed or not completely reviewed because they were on schedule and an annual status report had not been received or the most recent annual reports were unavailable.

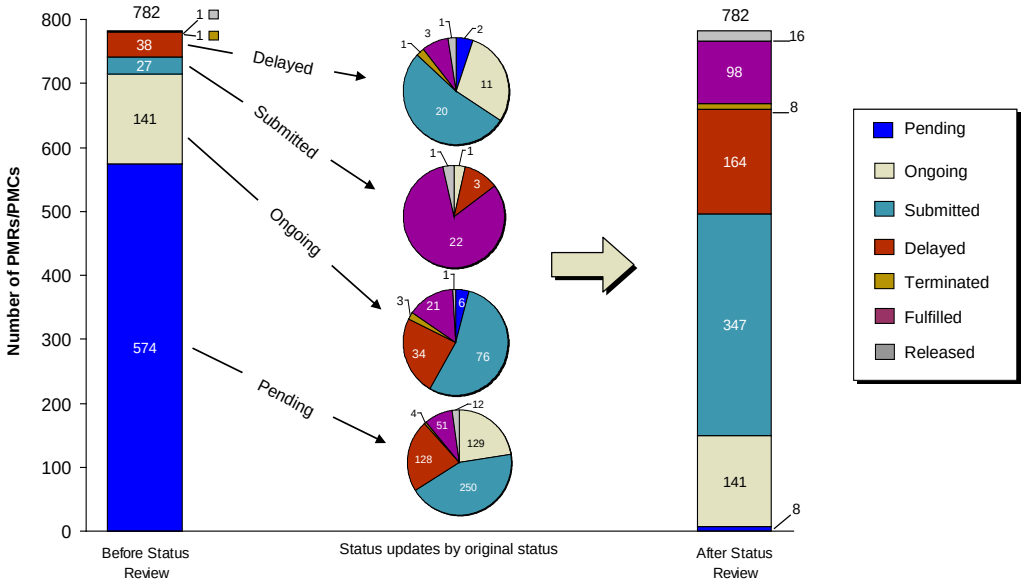
Exhibit 8: PMR/PMC Status Reviews



Notes: **PMRs/PMCs with an OK status were only reviewed when an annual status report (ASR) was received as part of the ASR review task.*
***Unknown Status indicates that a PMR/PMC without milestone dates or only a final report date was classified as Pending*
****47 out of 108 PMRs/PMCs not reviewed could not be reviewed due to an inability to obtain necessary documents.*

In examining the 782 PMRs/PMCs whose statuses required updates, 574 (73%) were incorrectly categorized as pending, 141 (18%) ongoing, 37 (5%) delayed, 27 (3%) submitted, 1 released, and 1 terminated (Exhibit 9). Most notably, nearly half of all PMRs/PMCs that were categorized with an inaccurate status were re-classified as submitted.

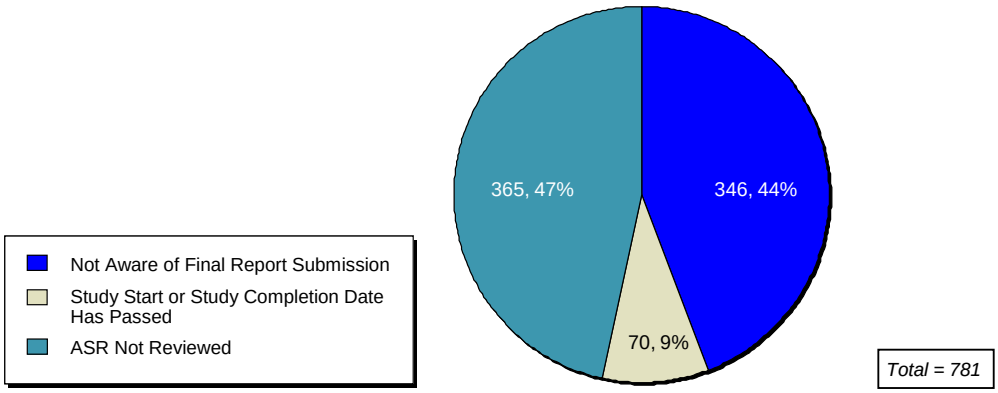
Exhibit 9: PMR/PMC Backlog Status Updates



Note: After the status review, one PMC status was updated from terminated to submitted and one PMC status was updated from released to fulfilled.

Status updates to the PMR/PMC database are typically made through one of three ways: completing and archiving annual status report summaries, notifying the PMR/PMC database manager of submissions received, or issuing properly-coded fulfillment or release letters to sponsors. The most common explanation for inaccurate status in the PMR/PMC database was PMR/PMC ASRs not being reviewed or the corresponding annual status updates not being entered in the FDA data systems (47%). Regulatory Project Managers (RPMs) unaware of final report submissions (44%) and lack of updates when study/trial start or finish milestones pass (9%) also contributed significantly to errors in the database (Exhibit 10). This last cause is difficult to address because there is no submission associated with either the study/trial start or study/trial completion milestones, so there is no trigger to update the status.

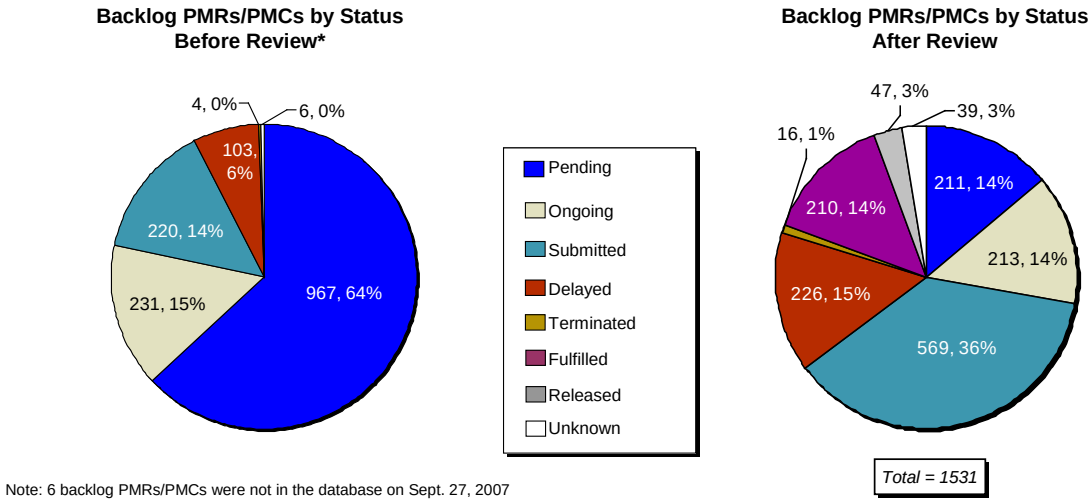
Exhibit 10: Source of PMR/PMC Status Error



The distribution of Backlog PMRs/PMCs statuses changed significantly between September 27, 2007 and the Backlog review data lock date. On the date FDAAA was enacted, most Backlog PMRs/PMCs were categorized as pending (64%), followed by ongoing (15%) and submitted

(14%) (Exhibit 11). After reviewing and updating the status for relevant PMRs/PMCs, the largest segment of Backlog PMRs/PMCs are accurately categorized as submitted (36%), followed by delayed (15%), ongoing (14%) and pending (14%). The percentage of pending PMRs/PMCs decreased from 64% to only 14%, but the PMRs/PMCs with submitted status increased from 14% to 36%. More than twice as many PMRs/PMCs were discovered to be delayed as compared to the status prior to the FDAAA enactment date. This significant pattern change could have a noteworthy impact on both industry and FDA. Previously, it appeared that most studies/trials had not yet been initiated, leading to public criticism of both FDA and the pharmaceutical and biotech industry. However, the updated statuses show that most PMRs/PMCs have been initiated, and more than half of them were either submitted with the final study/trial report, fulfilled or released. The largest segment of PMRs/PMCs is now awaiting FDA review of a sponsor-submitted final report.

Exhibit 11: Comparison of Overall Backlog PMR/PMC Status



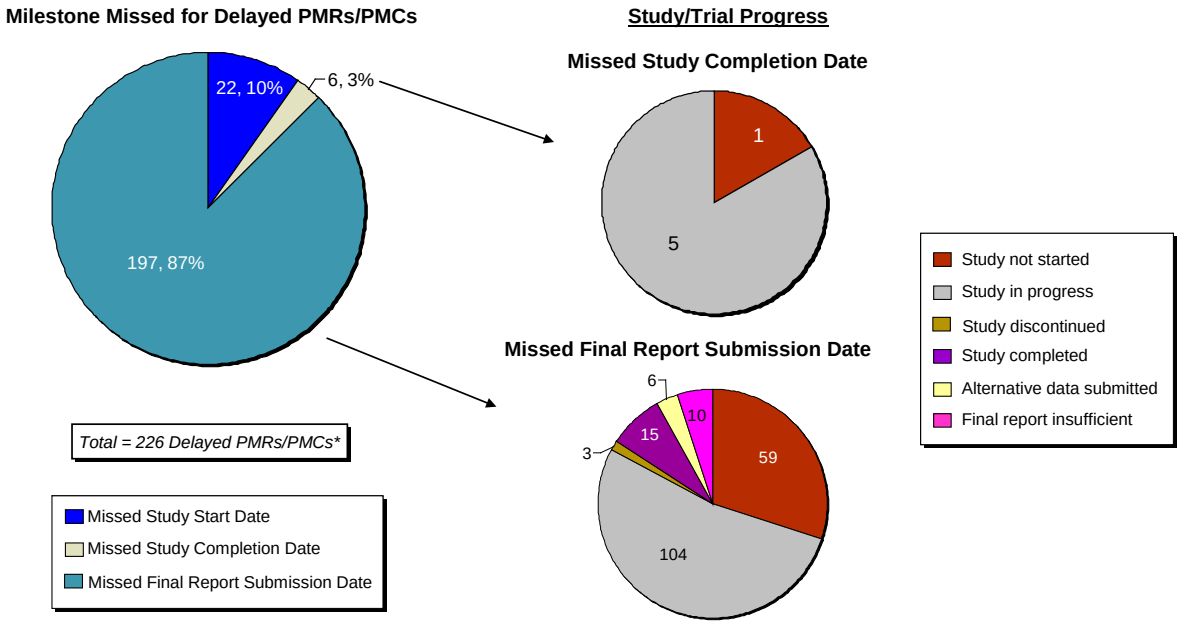
Note: 6 backlog PMRs/PMCs were not in the database on Sept. 27, 2007

4.3. Off-Schedule PMCs and PMRs

Off-schedule PMRs/PMCs are those that are not currently progressing according to the original study/trial schedule and are therefore classified as either delayed or terminated. The fact that these PMRs/PMCs are off-schedule could imply potential issues with the study/trial design or patient recruitment, and they may require additional investigation to determine if the study or trial is no longer feasible or relevant. The most common reason for delayed PMRs/PMCs was missing the agreed-upon deadline for submission of the final report. Delay in submission of the final study/trial report was the cause of 87% of delayed PMRs/PMCs while only 3% were delayed in completion of the study/trial (Exhibit 12). This large disparity is likely explained by the fact that only 14% of PMRs/PMCs have a study/trial completion milestone date, while 70% have a final report milestone date.[13] Furthermore, FDA does not require any regulatory correspondence from sponsors when studies/trials start or are completed. Instead, these milestones are often only reviewed after receipt of the annual status report, which may occur several months after the study/trial start or completion milestone date has occurred.

[13] Out of 1531 Backlog PMCs, 218 have study/trial completion dates, and 1073 have final study/trial report dates.

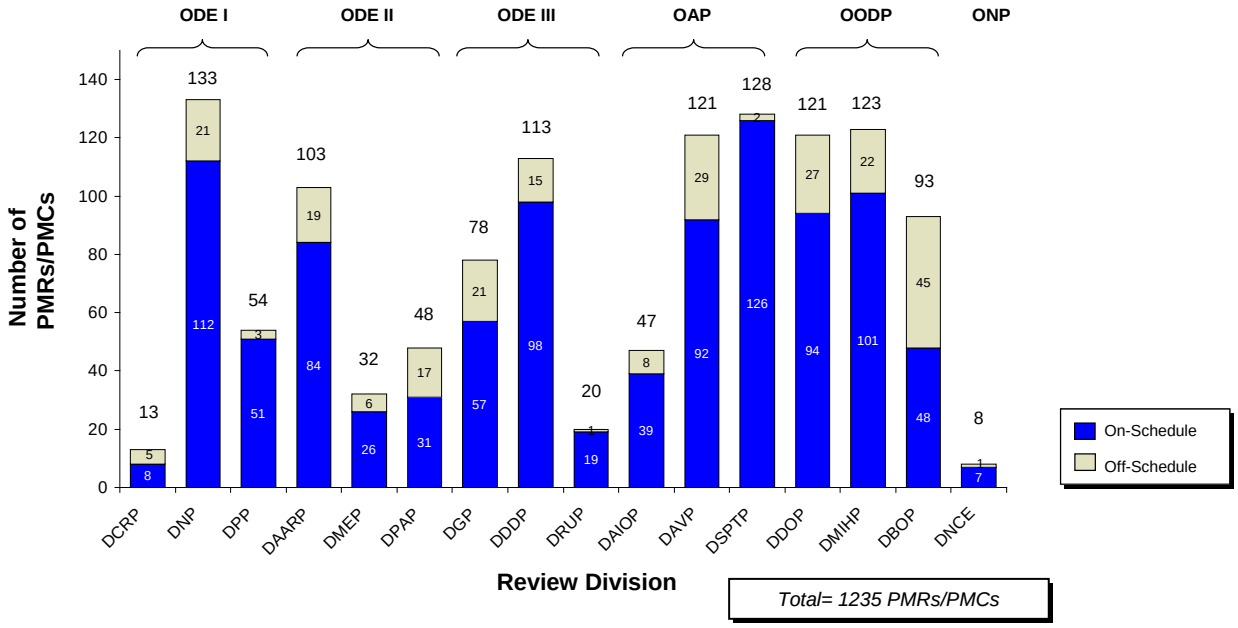
Exhibit 12: Study/Trial Phase of Delay for PMRs/PMCs with Delayed Status



*Note: *One delayed PMC was classified as delayed as of 9/27/07 based on a relative date tracked by the review division.*

Off-schedule PMCs were present in similar proportions across most review divisions/offices. Divisions with the most off-schedule PMCs were the Divisions of Biologic Oncology Products (DBOP),[14] Anti-Viral Products (DAVP), and Drug Oncology Products (DDOP) (Exhibit 13).

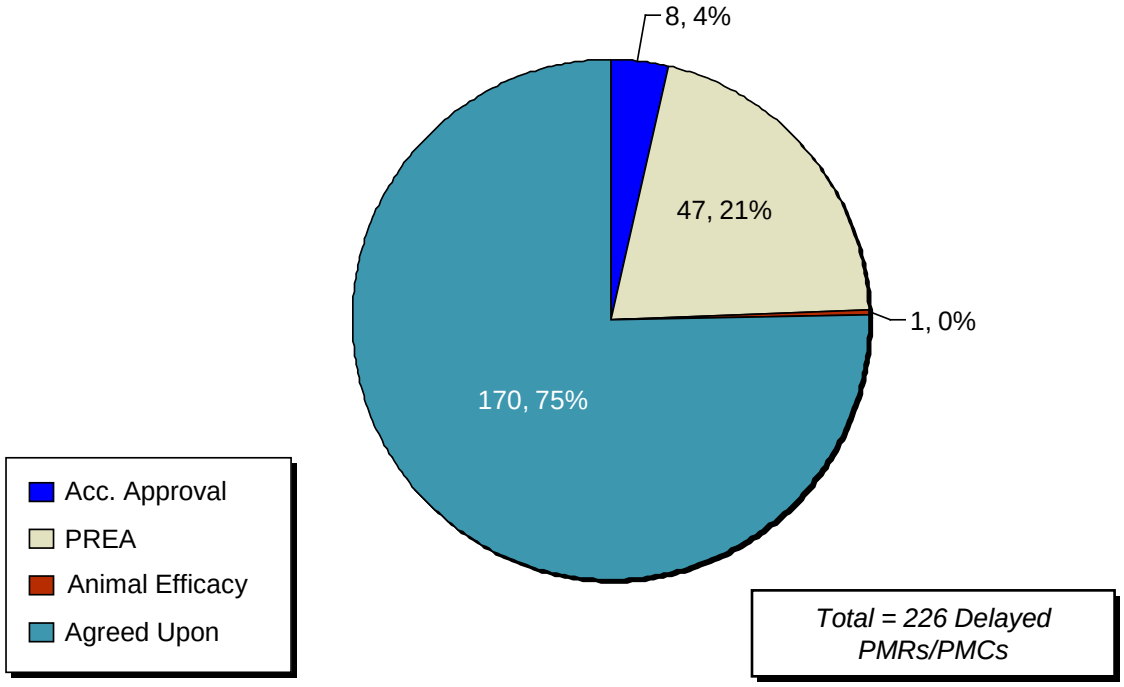
Exhibit 13: On- and Off-Schedule PMRs/PMCs by Review Division



[14] DBOP typically keeps a PMR/PMC classified as delayed if a final study/trial report was submitted but deemed insufficient to fulfill the PMR/PMC. This PMR/PMC remains open until alternative results are accepted by DBOP. This practice contributes to the higher proportion of off-schedule PMRs/PMCs compared to other review divisions.

Most delayed studies/trials were agreed-upon PMCs (75%) (Exhibit 14). Only 4% of delayed PMRs/PMCs were products with accelerated approval designation. In the overall Backlog (1531 PMRs/PMCs), 14% were PREA studies (Exhibit 7), while among delayed PMRs/PMCs, 21% were PREA PMRs.

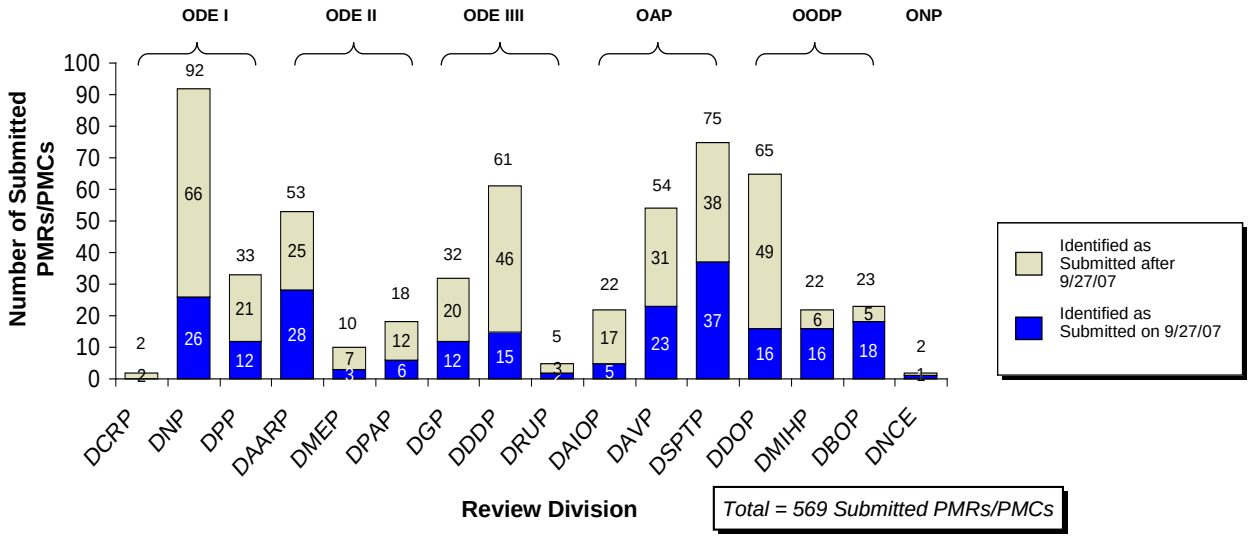
Exhibit 14: Delayed PMRs/PMCs



4.4. Submitted PMRs/PMCs

As discussed in section 4.2, the majority of PMRs/PMCs with status changes were updated to submitted. Of the submitted PMRs/PMCs, the Divisions of Neurology Products (DNP) and Special Pathogen and Transplant Products (DSPTP) had the greatest numbers (92 and 75, respectively) of reports to review, and more than half of them had not been identified as submitted before this study (Exhibit 15). These two divisions, along with the Divisions of Dermatology and Dental Products (DDDP), Drug Oncology Products (DDOP), and Anti-Viral Products (DAVP) had the greatest numbers of newly identified submitted PMRs/PMCs.

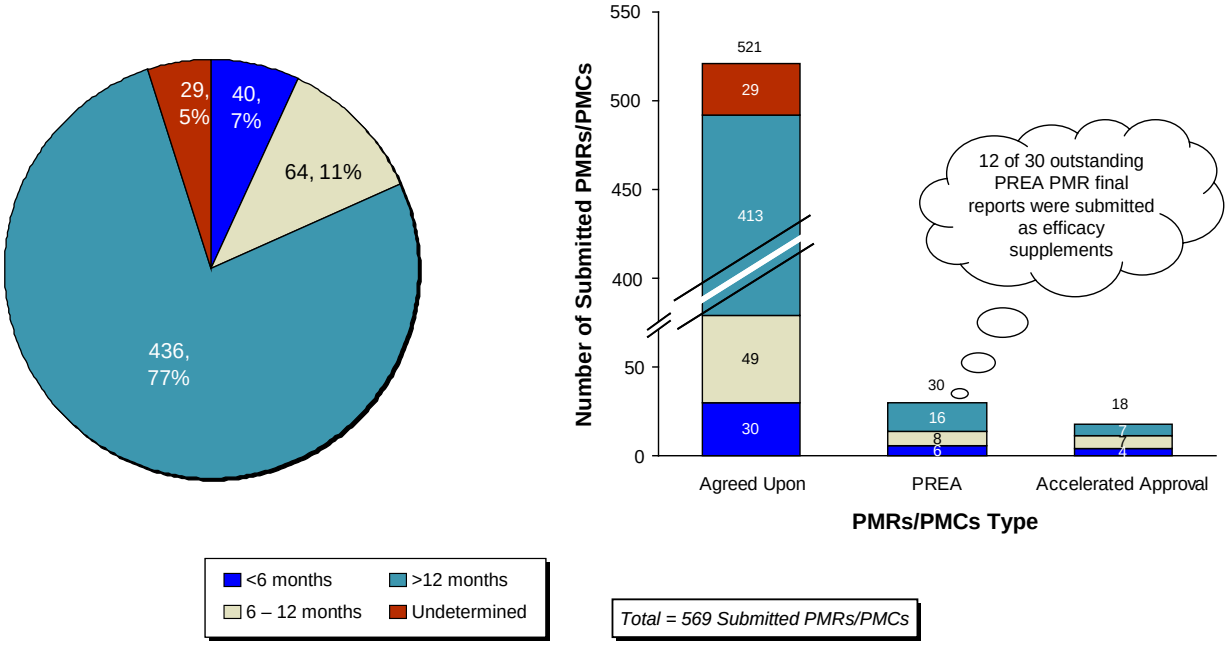
Exhibit 15: Final Reports Received by Division



FDA's internal goal for completing review of PMR/PMC final reports is 12 months, except in cases where the final report was submitted as part of a submission that must adhere to PDUFA goal dates.[15] Final reports for 77% of the PMCs classified as submitted were received more than 12 months ago, indicating that FDA misses their review deadlines more than half the time (Exhibit 16). Due to the challenges of competing priorities with PDUFA-driven deadlines, the large proportion of final reports that have not been reviewed within the target timeframe may be attributed to a lack of availability of review staff when final reports are received.

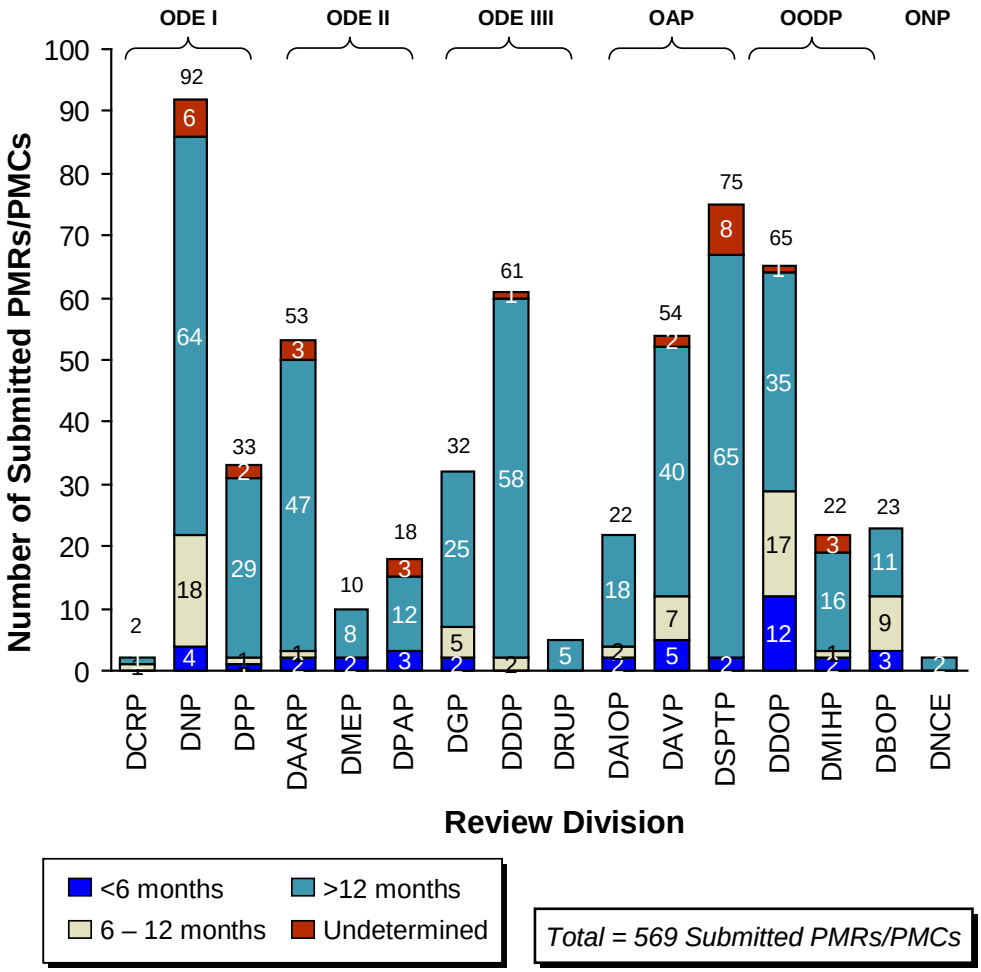
[15] The review timeframe for final study/trial reports is described in the Guidance for Industry, Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (February 2006). Final reports submitted as part of an efficacy supplement are subject to the PDUFA review goal date of six months.

Exhibit 16: Time Since Final Report Received



Consistent with the overall quantity of PMR/PMC final reports to be reviewed by Divisions of Neurology Products and Special Pathogen and Transplant Products, these divisions also have the largest number of final reports received more than 12 months ago. There were 70 PMR/PMC final reports in the Division of Neurology Products were received more than 12 months ago and 73 of in the Division of Special Pathogen and Transplant Products (Exhibit 17).

Exhibit 17: Time Since Final Report Received by Division



4.5. PMRs/PMCs Lacking Final Report Milestone Date

In developing PMRs/PMCs, FDA often collaborates with sponsors to identify specific milestone dates which should be established that are subsequently used to track the progress of the commitment and determine the status of the PMR/PMC. In the Backlog, there were 458 commitments that had no specific completion date or deadline associated with them, which has led these PMRs/PMCs to languish in a pending or ongoing status category indefinitely. These PMRs/PMCs either did not have a completion milestone at all, or had one that was a relative date[16] based on completion of a previous milestone (e.g., 12 months after study/trial start). The highest proportion of PMRs/PMCs lacking a completion date were agreed-upon PMCs, which comprised of 95% (404/424) of the no date/relative date commitments (Exhibit 18). This is consistent with expectations since most PMRs/PMCs in the Backlog were agreed-upon PMCs (82%, see Exhibit 7). In this case, relative dates do not pose a problem if they are associated with milestones that can be tracked, although tracking these milestones requires more effort than specified dates.

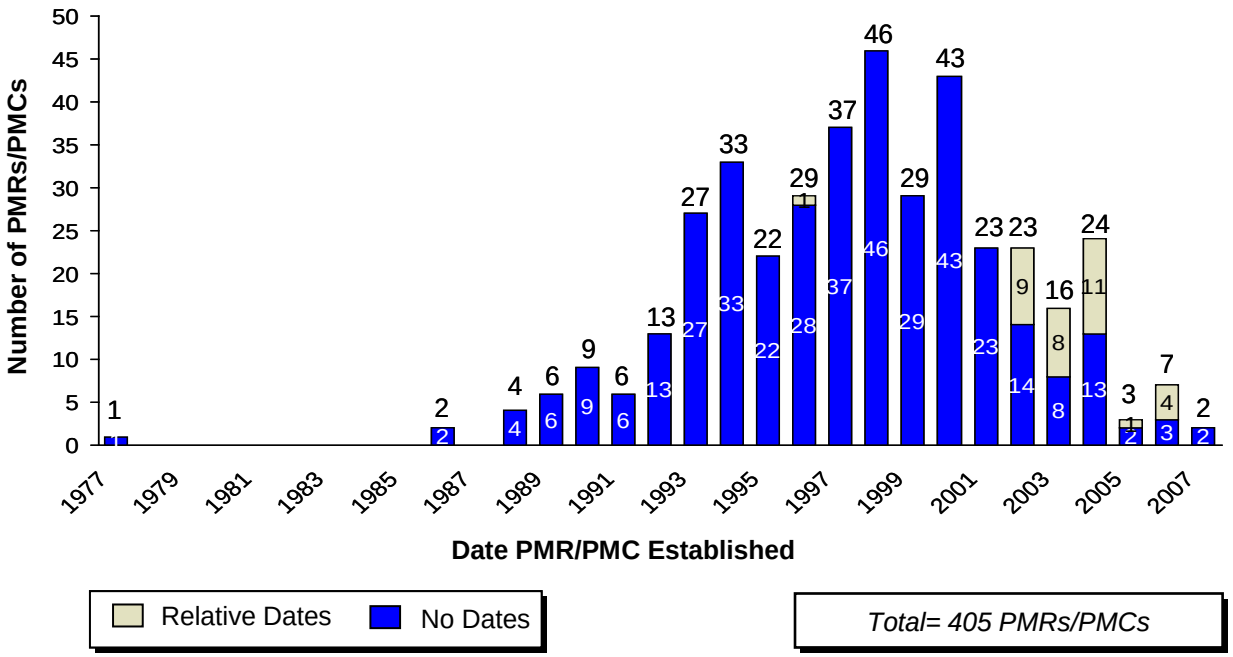
[16] Relative dates are not exact specified dates, but timelines for study/trial milestones based on completion of a previous milestone, e.g. 6 months after study/trial start date.

Exhibit 18: **PMRs/PMCs Lacking a Specific Completion Date**

	Relative Dates	No Dates
Accelerated Approval	2	12
PREA	2	7
Animal Efficacy	0	1
Agreed Upon	30	404
TOTAL	**34**	**424**

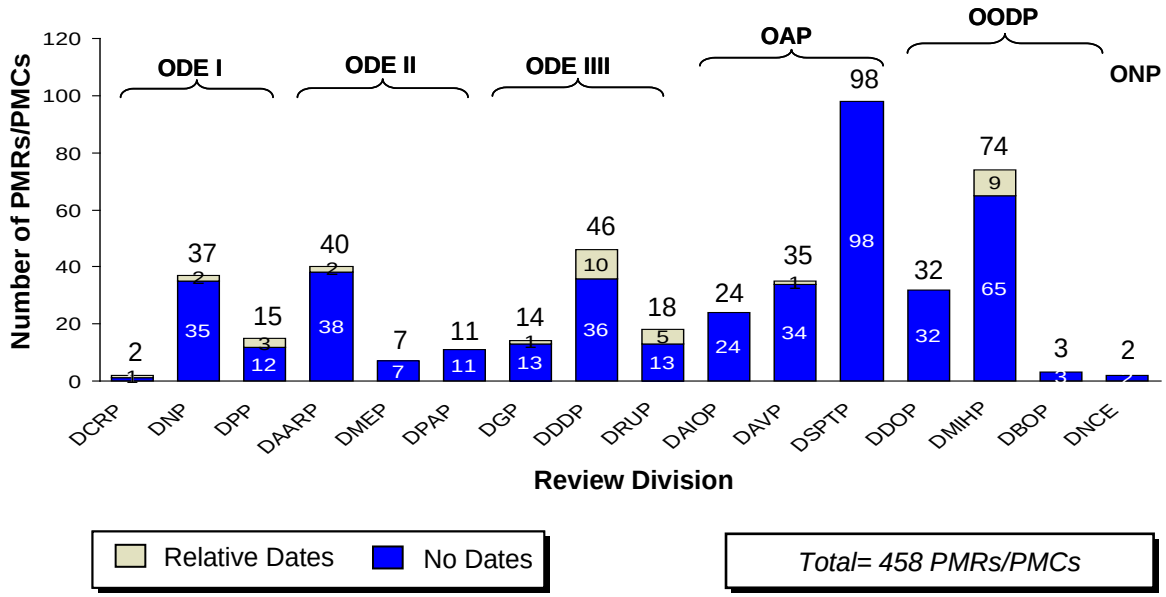
Nearly half (46%) of PMCs without completion dates were created more than 10 years ago (Exhibit 19). This pattern stands in contrast to the overall number of PMRs/PMCs by date established in the Backlog, which is skewed toward the most recent four years (Exhibit 5). The decrease in the number of PMRs/PMCs missing a completion milestone date suggests that FDA has improved its practices based on experience and wider adoption of PMR/PMC development policies.

Exhibit 19: **PMRs/PMCs with No Completion Date or Relative Completion Date by Year Established**



Two review divisions, the Division of Special Pathogens and Transplant Products and the Division of Medical Imaging and Hematology, had a substantially greater number of PMCs/PMRs without specific completion dates than other review divisions (Exhibit 20). This suggests a lack of uniformity in establishing completion milestone dates for PMRs/PMCs among divisions.

Exhibit 20: No Date PMRs/PMCs by Review Division

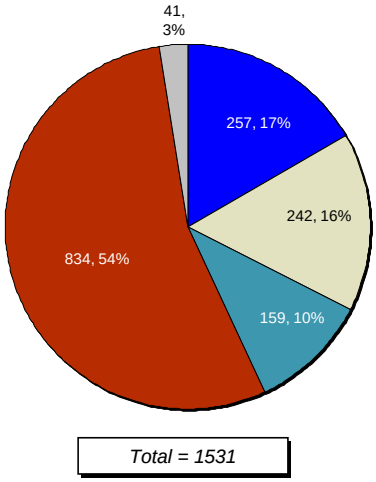


4.6. Backlog PMR/PMC Recommendations

The main objective of the Backlog review was to identify PMRs/PMCs for possible re-evaluation or closure (i.e., release or fulfill). Of the 1531 PMRs/PMCs in the Backlog, 1235 (81%) were reviewed and issued recommendations according to the prioritization scheme described in Appendix A (Exhibit 21). The remaining PMRs/PMCs were not issued recommendations because they were either closed (i.e., fulfilled or released) or the correct status was undetermined.[17]

[17] A PMR/PMC status was undetermined if the necessary documentation did not exist or could not be found to determine the correct status for a PMR/PMC that had passed a milestone date.

Exhibit 21. Backlog PMRs/PMCs by Prioritization for Review



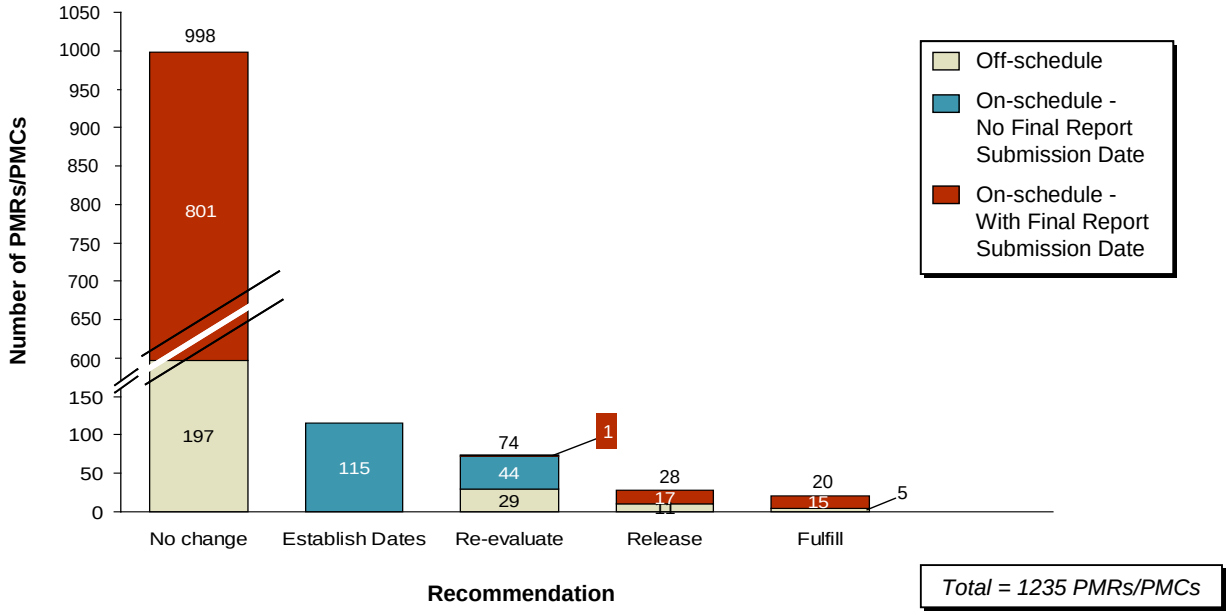
Legend	Category	Priority	Recommendation Process
	Off-schedule	High	Conducted thorough investigation of current activities
	On-schedule – No Final Report Submission Date	Medium	Researched recent activity within 2 years
	On-schedule – Existing Final Report Submission Date	Low	Reviewed FDA data systems for indication of Withdrawn by Commissioner status, Fulfilled letters, and Release letters
	Unknown	N/A	Not applicable
	Closed	N/A	Not applicable

PMRs/PMCs were recommended for no change if they were proceeding according to their original study/trial schedule, off-schedule but still in progress toward completion, or off-schedule but still relevant and feasible to conduct. Of the 1235 PMRs/PMCs evaluated for recommendations, the vast majority (81%, 997/1235) of Backlog PMRs/PMCs were recommended for no change. Only 74 (6%) were recommended for re-evaluation due to concerns over relevance or feasibility, which requires FDA to evaluate and determine the appropriate course of action (Exhibit 22). This finding suggests that most PMRs/PMCs are sufficiently feasible and relevant to be conducted and completed, and that the fact that there is a large number of open PMRs/PMCs does not indicate poorly-crafted commitments or requirements.

For those PMRs/PMCs that were off schedule, Booz Allen recommended no change for 81% (197/242) of them (Exhibit 22). Of the on-schedule PMRs/PMCs that lacked a final report submission milestone date, 72% (115/159) were issued a recommendation to proceed with the study/trial but establish a completion date, because the sponsor had reported on the status within the last two years. PMRs/PMCs identified for re-evaluation included 39% (29/74) off-schedule PMRs/PMCs, 59% (44/74) on-schedule PMRs/PMCs with no final report submission date, and a single PMC that was on-schedule with a final report submission date.[18] Of the PMRs/PMCs recommended for release, 39% (11/28) were categorized as off-schedule.

[18] The sponsor submitted a partial response to PMC 1 under the supplemental NDA which addressed the 1 – 2 year age range for the PMC, but not the 0 – 1 age range. The division developed a new PMC for the 0 – 1 age range under the parent NDA and left open PMC 1 under the supplemental NDA.

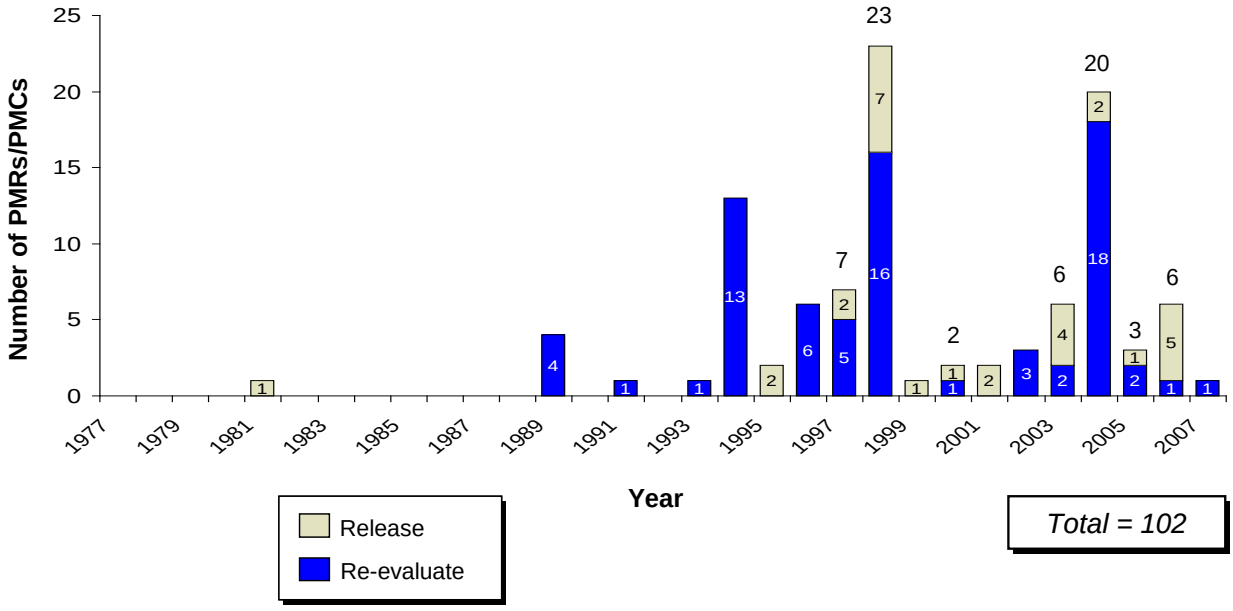
Exhibit 22. Backlog PMR/PMC Recommendations by Prioritization



Note: No recommendations were made for 257 closed PMRs/PMCs (i.e., fulfilled or released) or 39 PMRs/PMCs for which the status was unknown.

PMRs/PMCs recommended for release did not exhibit an age-related trend (Exhibit 23).

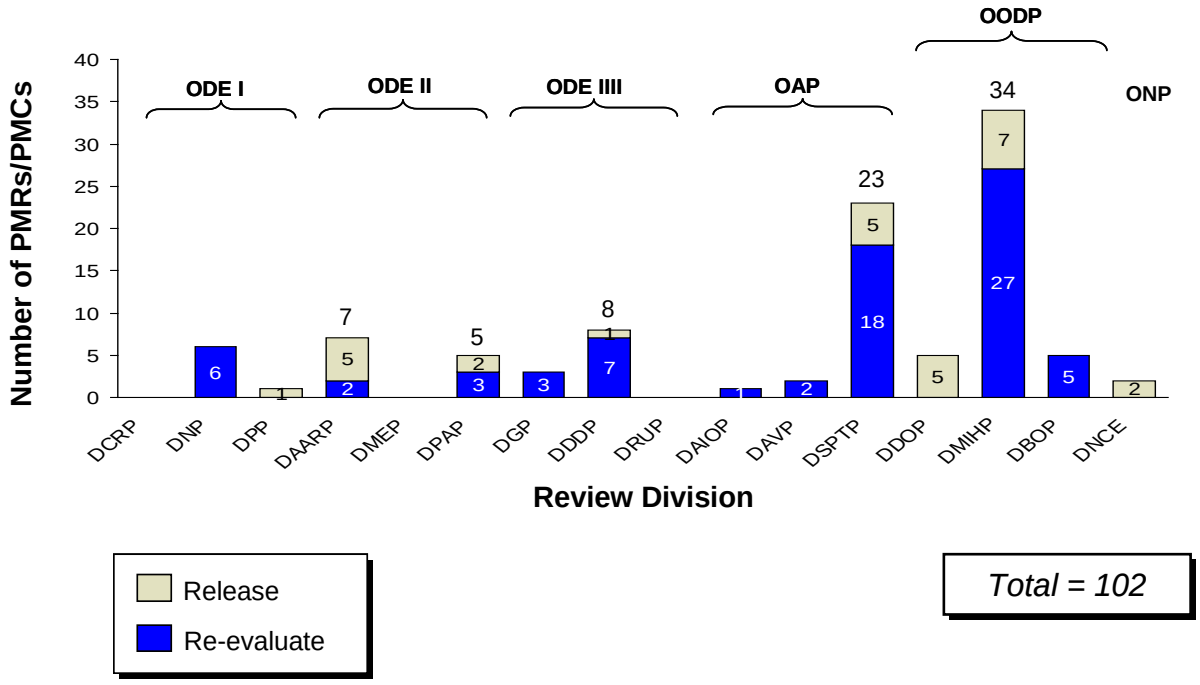
Exhibit 23: Re-evaluate and Release Recommendations by PMR/PMC Age



Most of the PMRs/PMCs recommended for re-evaluation and release were in the Division of Medical Imaging and Hematology Products (DMIHP) and the Division of Special Pathogen and Transplant Products (DSPTP) (Exhibit 24). Of those recommended for release, 25% (7/28) were in DMIHP in addition to the 36% (27/74) of PMRs/PMCs recommended for re-evaluation.

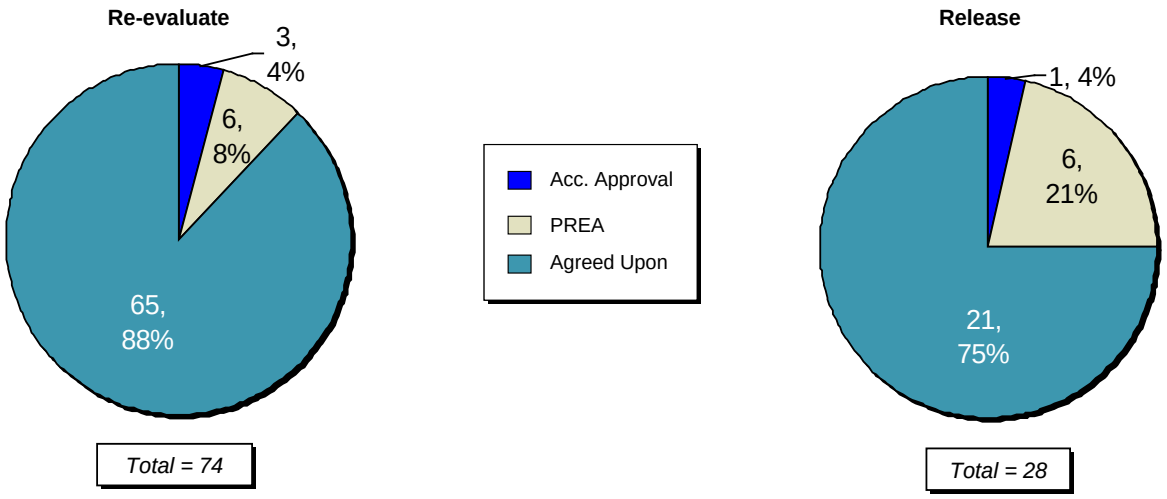
DSPTP was the division responsible for 18% (5/28) of the PMRs/PMCs recommended for release, as well as 24% (18/74) of those recommended for re-evaluation.

Exhibit 24: Re-evaluate and Release Recommendations by Review Division



Most of the studies/trials recommended for re-evaluation (88%) and release (75%) were agreed-upon PMCs (Exhibit 25).

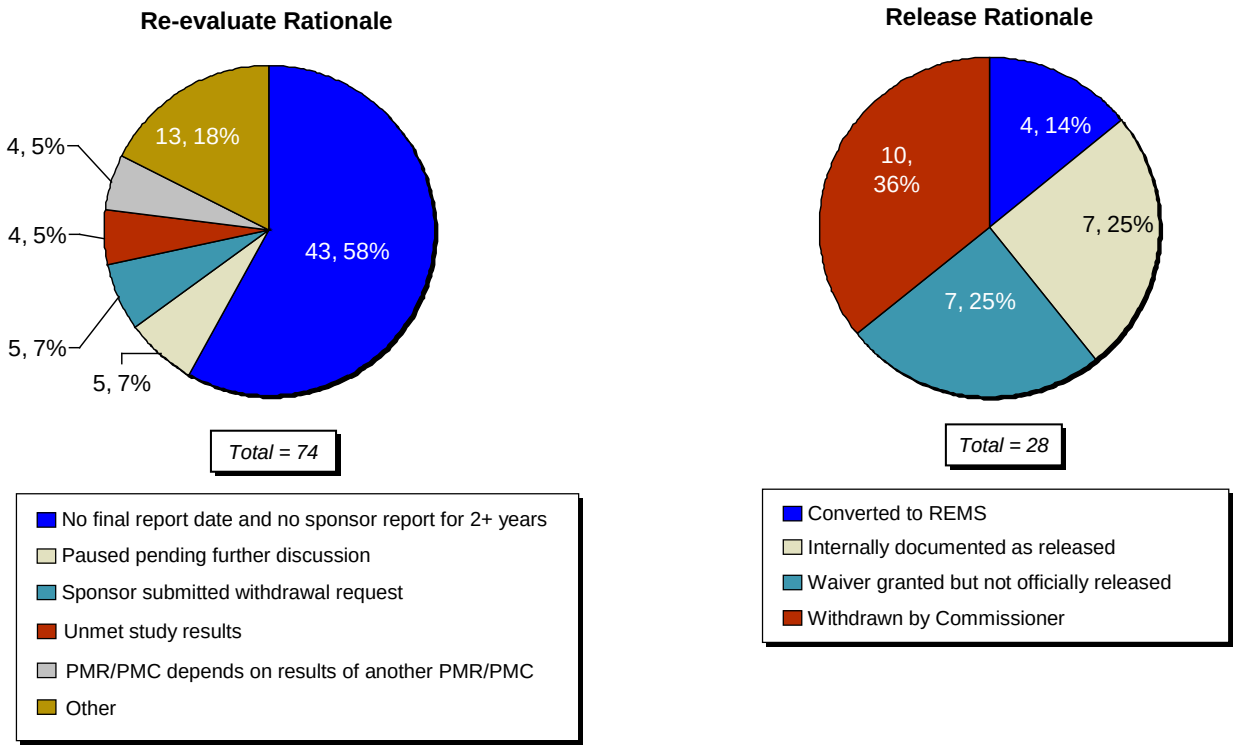
Exhibit 25: Re-evaluate and Release Recommendations



Note: There were no Animal Efficacy studies that were recommended for re-evaluation or release

The majority (58%) of PMRs/PMCs recommended for re-evaluation did not have final report submission dates and largest segment (36%) of the release recommendations were issued because the product was withdrawn from the market (Exhibit 26).

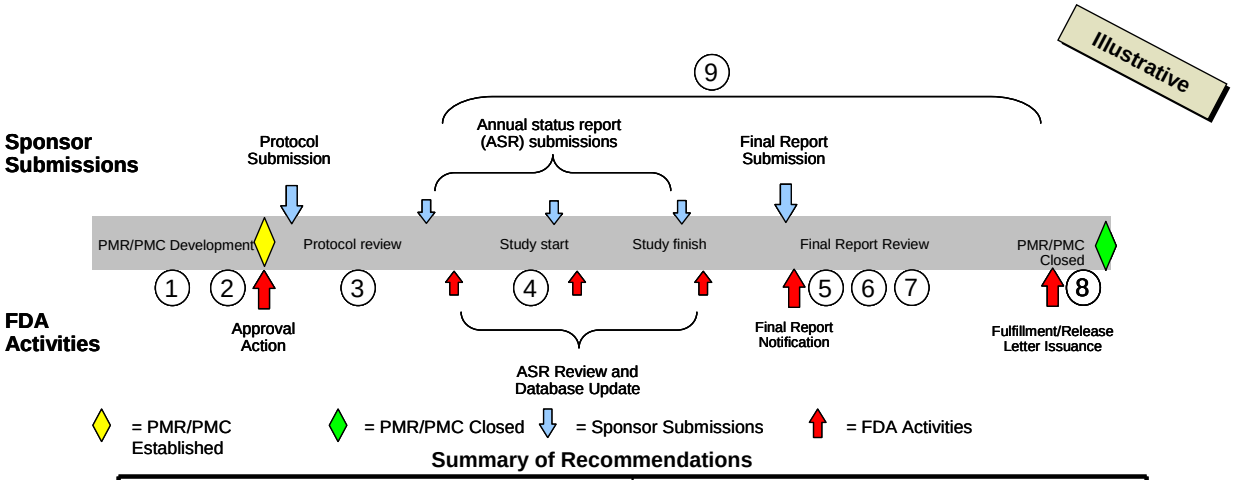
Exhibit 26: Reason for Recommendation



5. RECOMMENDATIONS

In the course of conducting and analyzing data from the Backlog review, Booz Allen developed a number of recommendations to address process issues, which span the PMR/PMC lifecycle. These recommendations focus on reducing the size of the PMR/PMC Backlog, facilitating the on-schedule completion of PMRs/PMCs, and alleviating problems that lead to tracking difficulties and inaccurate PMR/PMC statuses. The recommendations are shown below in Exhibit 29, along with their position with respect to an illustrative PMC lifecycle.

Exhibit 27. PMR/PMC Backlog Review Recommendations Summary



Summary of Recommendations

1	Write PMRs/PMCs to meet specific objectives, not specific protocols or studies	6	Improve compliance with notifying PMR/PMC PM when final reports received
2	Establish specific study start and final report milestone dates	7	Facilitate timely review of submitted final reports
3	Notify sponsors not to wait indefinitely for protocol review prior to study initiation	8	Correctly process fulfillment and release letters
4	Standardize sponsor ASR submission and streamline FDA ASR review	9	Record actual dates of milestone completion to better respond to requests and capture/understand PMR/PMC performance
5	Consistently send Dunner letters for late final reports		

1) Write PMRs/PMCs that meet specific objectives. Some PMRs/PMCs were written with reference to specific studies or protocols as opposed to defining study/trial objectives. This practice complicated PMR/PMC tracking and status updates when the sponsor conducted a different study/trial to satisfy the intent of the PMR/PMC. Booz Allen recommends that FDA develop PMRs/PMCs that describe a specific objective as opposed to specifying completion of a particular study/trial. This practice would provide flexibility and may increase compliance in fulfilling the commitment. This practice would also eliminate the need to consider revising a PMR/PMC when a sponsor satisfies a PMR/PMC with a different study/trial than initially planned.

2) Establish specific study/trial start and final report submission milestone dates. The use of study/trial schedule milestones varied throughout CDER, with respect to both the milestone (e.g., study/trial start) and the type of date (i.e., specific or relative). In order to simplify reporting and tracking for FDA and sponsors, FDA should consider issuing fixed (i.e., not relative) study/trial start and final report submission milestone dates for PMRs and PMCs. These two milestones are an important measure of the progress to complete the PMR/PMC and are linked to status updates. In cases where FDA continues to use relative milestone dates, the PMR/PMC databases should capture the actual dates of milestone completion and automatically calculate the date for subsequent milestones. FDA should consider creating a new mechanism (e.g., new submission type, PMR/PMC website functionality) to offer sponsors the option of notifying FDA of study/trial initiation. This new reporting strategy would allow sponsors and FDA to streamline the reporting process and improve the accuracy and compliance of PMR/PMC status updates. Accurate PMR/PMC tracking is essential, especially with the new enforcement authorities granted by FDAAA.

3) Notify sponsors not to wait indefinitely for FDA protocol feedback. Before beginning a postmarketing study/trial, sponsors typically submit protocols for FDA review. In some instances sponsors do not subsequently initiate the study/trial in a timely manner, apparently because they mistakenly believe FDA is obligated to respond to a submitted protocol before the study/trial is initiated. This misunderstanding has occasionally resulted in unnecessary delays for PMR/PMC study/trial conduct with the sponsor explaining in an annual report submission that it is awaiting FDA protocol feedback before proceeding with the study/trial. To address this, FDA should compose a template letter to notify sponsors that although FDA intends to review the protocol, the sponsor should not necessarily wait for feedback to proceed with study/trial initiation. Sponsors should be reminded of the study/trial schedule in this letter, as well as the fact that they will be held accountable to those milestone dates, regardless of when FDA provides feedback on the protocol.

4) Standardize sponsor annual status report submissions and streamline FDA annual status report review. In this analysis, nearly half of inaccurate PMR/PMC statuses were attributed to PMR/PMC ASRs not being reviewed or reviews not being entered into FDA data systems (for NDAs) or communicated to the PMR/PMC database manager (for BLAs). Booz Allen observed many instances in which the sponsor did not provide complete or sufficient information to determine the correct status. These cases required a substantial additional effort to determine the true PMR/PMC status. To improve PMR/PMC reporting consistency and compliance, sponsors should be required to complete an interactive form developed by FDA that captures all of the values required to determine the accurate status of a PMR/PMC. This form will help sponsors standardize the PMR/PMC reporting process within the company allowing for economies of scale. In tandem, FDA should create processes and increase functionality of current FDA data systems (e.g., drop down menus in DARRTS) to streamline the ASR review and status update process.

5) Send Dunner letters for missed Annual Status Report and final report milestones. When a PMR/PMC Annual Status Report is outstanding and overdue, the review division is expected to generate a Dunner letter notifying the sponsor of the delinquency. However, Booz Allen observed that this practice is not widely implemented by the review divisions. Furthermore, an additional Dunner letter should be sent to remind sponsors of a missed final report milestone date. This proactive tracking and communication may encourage greater compliance by sponsors with timely submission of PMR/PMC documents, which in turn would result in a more accurate PMR/PMC database. Further, FDA is now empowered to enforce compliance with FDAAA PMR study/trial milestones with civil penalties.

6) Improve compliance with updating PMR/PMC database when final report submissions are received. Booz Allen has observed that PMC/PMR status is not consistently updated in the PMR/PMC database when FDA receives a final study/trial report. Notably, many PMRs/PMCs that were classified as pending or ongoing had final reports already submitted to FDA. This gap should be reconciled by improving the process (e.g., create an alert in current FDA data systems) that RPMs follow to notify the PMR/PMC Project Manager when a sponsor submits a final report. Alternatively, FDA could expand the functionality of the public PMR/PMC database to allow sponsors to link submitted final reports to specific PMRs/PMCs.

7) Facilitate timely review of submitted final reports. Although it initially appeared that the majority of open PMRs/PMCs had not been initiated, this review reveals that the real PMR/PMC Backlog is the more than 500 PMR/PMC final reports that FDA needs to review to close out these PMRs/PMCs. FDA should proactively facilitate the review of these final reports. The overall approach to facilitating and managing the review of the PMR/PMC final reports should

consist of four steps: prioritizing reports for review, distributing reports to the appropriate reviewer or RPM, tracking the progress of the reviews, and carrying out certain follow-up actions as needed.

8) Accurately process outgoing fulfillment and release letters. Booz Allen discovered that some status errors were a direct result of letters designed to satisfy multiple goals (e.g., supplement approval and PMR/PMC fulfillment) that were incorrectly or incompletely processed in FDA data systems. If the letter is not correctly linked to the appropriate incoming PMR/PMC submissions and processed, the open submission may not be closed out and the PMR/PMC status may not be updated to the correct status (i.e., fulfilled or released). In order to inform staff of the proper linking and processing rules for outgoing submissions, FDA should either provide training material to staff or hold a short training seminar to highlight the correct linking and processing rules for these dual purpose letters. These small initiatives will help reduce PMR/PMC status errors resulting from improper assignments in FDA data systems.

9) Capture actual dates of milestone completion. FDA frequently receives requests for information about PMRs/PMCs and their current status, both from within the FDA and externally (e.g., Government Accountability Office (GAO), media outlets, members of Congress). These requests require FDA to manually collect much of the necessary information since only study/trial schedules with projected completion dates are currently tracked in the PMR/PMC database. Booz Allen recommends that FDA record actual dates of study/trial milestone progress in the PMR/PMC databases, such as when patient enrollment actually started or the final report was submitted. By inputting these values, FDA will be able to quickly respond to a request received from a given party, more easily track PMRs/PMCs with relative milestone dates, and have more information on hand about the history of the conduct of the PMR/PMC.

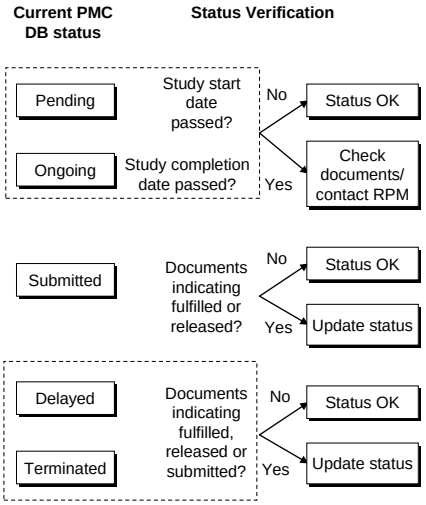
Appendix A: Detailed Procedures and Approach for the PMR/PMC Backlog Review

This appendix provides additional detail around the methods and processes for updating or verifying the correct status and conducting a review of the Backlog PMRs/PMCs.

PMR/PMC Status Updates

Before the Backlog PMRs/PMCs could be prioritized for review, a current and accurate status was determined for all PMRs/PMCs with either an incorrect or uncertain status.[19] PMRs/PMCs with an incorrect status classification were identified by comparing the current status in the internal PMR/PMC database with the phase in the PMR/PMC lifecycle (Exhibit 1) based on the milestone dates established in the product's approval letter. This evaluation identified PMRs/PMCs with a current PMR/PMC database status inconsistent with the original milestone dates (Exhibit 28). For submitted studies/trials, the status was considered correct unless there was documentation in the annual status report or FDA systems indicating that it had been fulfilled or released. Similarly, delayed and terminated PMRs/PMCs were considered accurately classified unless there was documentation or communications in the ASR or FDA systems indicating that the study/trial was ongoing, submitted, fulfilled or released.

Exhibit 28. Approach for Verifying PMR/PMC Database Status



After determining which PMRs/PMCs had incorrect or uncertain statuses, FDA data systems (e.g., DSS, DFS, RMS BLA) and internal documents (e.g., reviews, memos, letters to sponsors, meeting minutes) along with sponsor submissions (e.g., final study/trial reports, annual reports) were analyzed to ascertain the correct status of the PMR/PMC. Since there is no formal documentation received when a study/trial either begins or ends, Booz Allen contacted the RPM to verify the status with the sponsor if a study/trial start or study/trial finish milestone passed. The gathered data were stored in a data collection instrument (DCI), which was also used to

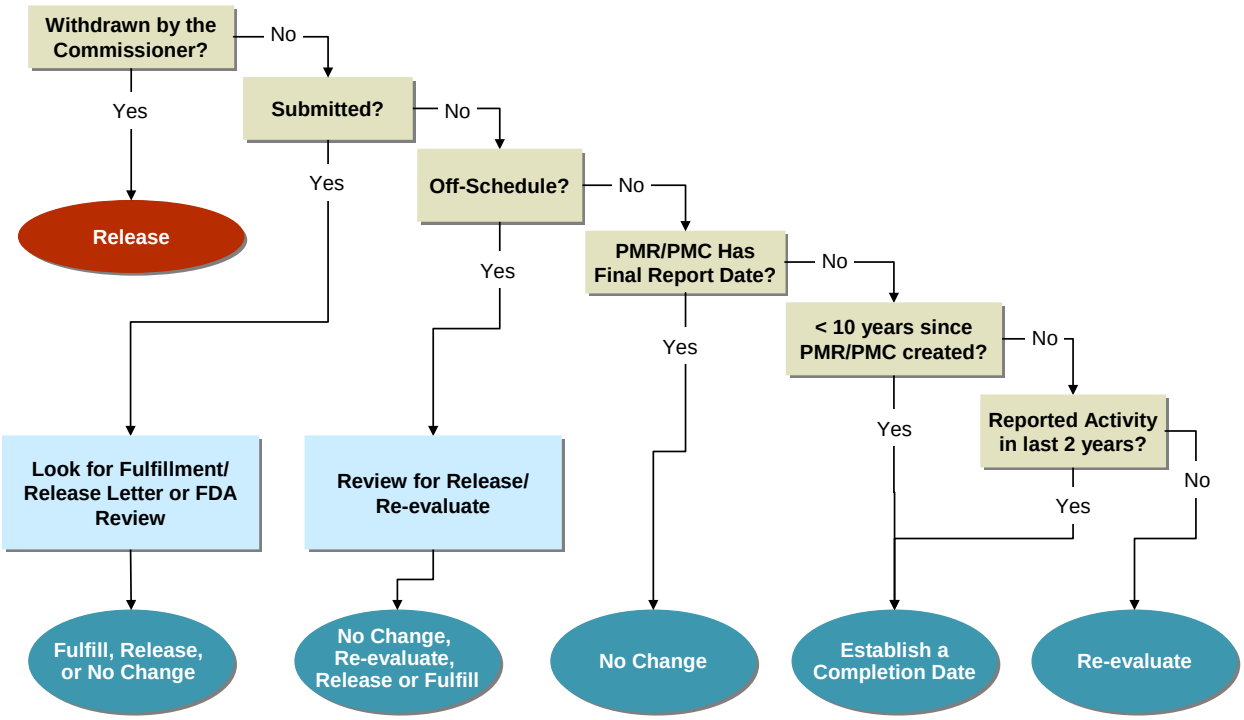
[19] Any PMR/PMC that was classified as pending in the PMR/PMC database, and had either no milestone dates or only a final study/trial report date was considered to have an uncertain status.

track the progress of the full Backlog review. Also during this phase of the task, PMRs/PMCs lacking critical milestone dates were identified and investigated to determine if dates were ever established. After determining the correct status for all open PMRs/PMCs for a product, a PMR/PMC summary sheet was distributed bi-weekly to the TAG and review divisions for status verification. After receiving confirmation that the status updates were correct, they were communicated to the FDA staff responsible for updating the internal PMR/PMC databases.

Backlog PMR/PMC Review

Once the accurate statuses were determined, the Backlog PMRs/PMCs were prioritized for detailed review (Exhibit 29). Based on this prioritization scheme, certain PMRs/PMCs were evaluated for potential re-evaluation or release.

Exhibit 29. Prioritization Scheme for Determining Candidates for Revision or Release



As a first step, PMRs/PMCs that were withdrawn by the Commissioner were recommended for release, since the product could not be marketed and would need to go through the full approval process again in order to be marketed. PMRs/PMCs with a status of submitted were also reviewed to determine if there was a release or fulfill letter issued, or an internal review indicating that one should be issued. Off-schedule PMRs/PMCs were classified as high priority for in-depth review because these PMRs/PMCs had missed critical agreed-upon milestone dates, suggesting that there may be a problem with the study or trial. Booz Allen assumed that on-schedule PMRs/PMCs did not require consideration for re-evaluation or release since they were proceeding according to the original schedule without indication of a problem. Those lacking a final report submission milestone date were designated as moderate priority for review. If the PMR/PMC was more than ten years old[20] and there had been no activity reported

[20] The ten year threshold was determined through discussion with the TAG.

for the PMR/PMC by the sponsor over the last two years, the PMR/PMC was recommended for re-evaluation. These criteria were determined because it seemed likely that an older study or trial may no longer be relevant or feasible after more than ten years of post-market experience, particularly if the sponsor is not reporting on it. PMRs/PMCs without a final report submission date that did not meet the criteria for re-evaluate were recommended for establishment of completion dates so that the status could be more accurately and proactively tracked in the future.

Within the group of PMRs/PMCs that were prioritized for review, accelerated approval PMRs/PMCs were evaluated first because of their public health significance in verifying clinical efficacy.

Recommendation Scenarios

Throughout the course of the Backlog review, certain scenarios were consistently encountered. These scenarios, shown in Exhibit 30, were documented, along with standard corresponding recommendations, to promote consistency in the review.

Exhibit 30. PMR/PMC Backlog Recommendation Scenarios

Scenario	Recom-mendation	Standard Approach	Rationale
Reviewer has internally documented a review of the PMC submission and that the PMC was fulfilled	Fulfill	Recommend review division issue a fulfill letter to sponsor and close the PMC	As the PMC has been reviewed and agreed to be fulfilled, notification should be sent to the sponsor and the PMC should be closed
A waiver (e.g., PREA) was granted but the PMC has not been officially released	Release	Recommend the review division issue a release letter.	Since the PMC has been waived, FDA should send the sponsor a release letter and close the PMC.
Converted to REMS	Release	Recommend the review division issue a letter outlining the REMS and release the PMC.	The PMC is identified as a potential REMS.
Reviewer has internally documented agreement with a sponsor request for PMC release	Release	Recommend review division issue a release letter	As the PMC has been reviewed and agreed to be released, notification should be sent to the sponsor and the PMC should be closed
The product has been withdrawn by the commissioner	Release	Recommend the review division issue a release letter.	Since the PMC has been waived, FDA should send the sponsor a release letter and close the PMC.
Contingency PMC	Re-evaluate	Review the original PMCs and recommend the review division to re-evaluate the contingency PMC if the original PMC is on hold awaiting FDA action, otherwise recommend for no change.	If the contingency PMC is delayed awaiting FDA's evaluation of the original PMC, the contingency PMC should be re-evaluated.
FDA has revised the	Re-evaluate	Recommend the review division	PMC description and/or

Scenario	Recom-mendation	Standard Approach	Rationale
PMC and/or proposed new timelines		re-evaluate the PMC and determine if it should be released and re-written or retained.	timelines have been revised extensively by FDA.
No activity has occurred on an old (i.e., >10 years) PMC	Re-evaluate	Recommend the review division re-evaluate the need for PMC and contact sponsor to discuss study/trial status and anticipated milestones	After lengthy postmarketing period, studies/trials originally proposed may no longer be necessary
Paused pending further discussion	Re-evaluate	The study/trial is on hold or idle pending FDA and sponsor further conversation. Therefore, the review division should re-evaluate the PMC to determine if it can be resolved with no change or it should be revised if it's still in need.	The sponsor and FDA are in negotiations and the studies/trials cannot be completed until the two come to an agreement.
Sponsor has requested market withdrawal, but FDA has not responded	Re-evaluate	Sponsors often stop conducting the PMCs if the product is withdrawn from the market. The review division should issue an acknowledgement letter to facilitate the withdrawal process. The PMC should be re-evaluated to determine if the PMC can be released after it has been formally withdrawn.	The sponsor requested withdrawal of the application, so the PMC may no longer be necessary.
Sponsor has requested release from PMC and there is no indication that the study/trial is proceeding	Re-evaluate	Classify PMC as terminated only if there is documented evidence the study/trial had started. Recommend the review team to review request for release	Terminated status is interpreted to mean a study/trial was stopped after at least some patients had enrolled.
Unmet results	Re-evaluate	The review division should re-evaluate the PMC to determine whether FDA should release the current PMC and issue a new PMR/PMC, or keep the PMC open and issue a new PMR/PMC.	Even though the results were insufficient to satisfy the PMC as fulfilled, the PMC should be re-evaluated to see if a revision is necessary.
PMC lacks a final report date, but recent activity has occurred on an old (i.e., >10 years) PMC	Establish a Date	• Ensure milestone dates were never established (e.g., in first ASR) • Work with review team to establish a date then request the sponsor to implement the new schedule	Even though the PMC has been created for a while, the recent activities demonstrate the PMC is in progress
PMC lacks final report date, but is less than 10 years old	Establish a Date	• Ensure milestone dates were never established (e.g., in first ASR) • Work with review team to establish a date then request the sponsor to implement the new schedule	PMCs without milestones are difficult to track, and cannot be satisfied and closed

Scenario	Recom-mendation	Standard Approach	Rationale
Due to difficulty with patient enrollment, FDA plans to allow different studies/trials to be submitted in support of the PMC	No Change	Look for the correspondence that documents the agreed upon alternative studies/trials and FDA should note in eventual fulfillment letter that the replacement studies/trials did meet the original objectives.	Studies/trials that support the intended PMC objective can be submitted to support fulfillment of the PMC.
Final study/trial report was submitted less than 12 months ago, but not reviewed	No Change	• Confirm FDA receipt of study/trial report and identify document location (e.g., in EDR or Document Room). Request from offsite document room if necessary. • Remind division PMC Tracking Coordinator of outstanding submissions needing review	The final study/trial report should be reviewed within 12 months of receipt.
Final study/trial report was received more than 12 months ago	No Change	• Confirm FDA receipt of study/trial report and identify document location (e.g., in EDR or Document Room). Request from offsite document room if necessary. • Remind division PMC/PMR Tracking Coordinator of outstanding submissions needing review	FDA guidance recommends final reports be reviewed within 12 months of receipt
PMC is on-schedule and has a final report date	No Change	No immediate action	The PMC is progressing on schedule.
Sponsor has requested a waiver (e.g., PREA) but FDA has not responded	No Change	FDA should evaluate the waiver request and determine to grant or deny the request, and inform the sponsor.	Even though the sponsor has requested a waiver, the PMC may still be necessary.
Study/trial start date has passed with no indication of whether sponsor has initiated the study/trial and ASR not yet received.	No Change	Review division should contact the sponsor to determine if the study/trial has started, and classify as ongoing or delayed.	No mechanism for sponsor to notify FDA of study/trial start other than ASR, which could lead to long time of inaccurate status
The study/trial is delayed but in progress	No Change	No immediate action	Even though the status is delayed due to the sponsor missing a milestone date, the study/trial is in progress.

Appendix B: Pilot Study Products

A pilot study of the Backlog review process was conducted to test and refine the data gathering and analysis approach to be employed in the full Backlog review. A representative sample of ten products (including the original application and all associated supplement applications) with PMRs/PMCs in the Backlog was chosen, based on the criteria in Exhibit 31 for the full pilot cohort:

Exhibit 31. Pilot Study Cohort Selection Criteria

Category	Selection Factor
Product Characteristics	• Large number of PMRs/PMCs • Wide range of years since product approval
Review Characteristics	• Mixture of Review Divisions • Mixture of BLAs and NDAs
PMR/PMC Profile	• Mixture of PMR/PMC types (e.g., safety, efficacy, pharmacology) • Mixture of PMRs and PMCs
PMR/PMC Schedule	• Mixture of current status (e.g., pending, ongoing, submitted, delayed, terminated) • Complete and incomplete study/trial schedules (i.e., milestone dates for study/trial start, study/trial finish, and final report submission)

Based on these criteria, the ten products listed in Exhibit 32 were selected for the Pilot Study.

Exhibit 32. Pilot Study Product Cohort

		506B PMRs/PMCs		
NDA/ BLA	Review Division	Req.	Agreed	Approval Year
NDA1	Special Pathogen and Transplant Products	0	6	1990
NDA2	Medical Imaging and Hematology Products	0	7	1994
NDA3	Psychiatry Products	0	4	1997
	Psychiatry Products	1	0	2004
	Psychiatry Products	1	0	2004
	Psychiatry Products	1	0	2006
NDA4	Dermatology and Dental Products	0	2	2001
	Dermatology and Dental Products	0	1	2006
NDA5	Antiviral Products	0	7	2002
	Antiviral Products	2	0	2006
	Antiviral Products	0	4	2006
NDA6	Drug Oncology Products	2	1	2004
NDA7	Cardiovascular and Renal Drug Products	1	1	2005
BLA1	Biologic Oncology Products	1	4	1999
BLA2	Gastroenterology Products	2	1	2003
BLA3	Anesthesia, Analgesia and Rheumatoid Products	1	3	2005

Appendix C: Office of New Drugs Review Division Key

Exhibit 33. Division Abbreviation Key

Division Abbreviation	Full Division Name
DCRP	Division of Cardiorenal Products
DNP	Division of Neurology Products
DPP	Division of Pulmonary Products
DAARP	Division of Anesthesia, Analgesic, and Rheumatology
DMEP	Division of Metabolic and Endocrine Products
DPAP	Division of Pulmonary and Allergy Products
DGP	Division of Gastroenterology Products
DDDP	Division of Dermatology and Dental Products
DRUP	Division of Reproductive and Urology Products
DAIOP	Division of Anti-Infective and Ophthalmology Products
DAVP	Division of Anti-Viral Products
DSPTP	Division of Special Pathogen and Transplant Products
DDOP	Division of Drug Oncology Products
DMIHP	Division of Medical Imaging and Hematology Products
DBOP	Division of Biologic Oncology Products
DNCE	Division Nonprescription Clinical Evaluation