Food and Drug Administration

CDER Analysis, Evaluation and Technical Assistance

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Deliverable 6:
Final Report on the PMR/PMC Backlog Review

March 12, 2010

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 authority to require sponsors of marketed drug and biologic products to conduct and report on their postmarketing studies and 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 to conduct after approval of the product. PMCs are typically designed to gather additional information about product safety, efficacy, or optimal use, and FDA has determined through a carefully deliberated process that the information 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 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. Section 921 of FDAAA added a requirement for FDA to review the entire Backlog of postmarketing requirements and commitments on an annual basis to determine which requirements/commitments should be revised or released. The objectives of this annual task were to:

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

For the first annual Backlog review, completed and documented in a final report dated April 10, 2009, FDA queried internal PMR/PMC tracking systems on September 30, 2007 to produce a list of open non-Chemistry, Manufacturing, and Controls (CMC) PMRs and PMCs, which was modified based on identification of additional PMRs/PMCs. The review was based on a cohort of 1531 open PMRs/PMCs that were part of the PMR/PMC Backlog as of September 27, 2007. During the course of the second annual review, Booz Allen discovered additional PMRs/PMCs that were erroneously included in or excluded from this group. After accounting for these issues, the actual PMR/PMC Backlog as of September 27, 2007, consisted of 1551 open PMRs/PMCs. 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 the prioritization scheme developed during the first annual review and used to develop recommendations. Recommendations will be validated by review division advisory groups and tracking coordinators, who will accept or revise the recommendations.

Status Progression Between Reviews
During its lifecycle, a PMR/PMC will either progress through the traditional pathway (i.e., pending, ongoing, submitted, fulfilled) or fall off schedule and become either delayed or terminated, based on progress made against established milestones. Additionally, FDA may decide that the PMR/PMC is no longer feasible or necessary and release the

[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).

requirement/commitment before it has been completed. In the first annual review, the focus was placed on determining the accurate, current status for PMRs/PMCs in the Backlog because 35% (542/1531) of the PMRs/PMCs were immediately identified as being classified under an incorrect status category due to inconsistencies with the milestones. Based on this comprehensive status review, the distribution of Backlog PMR/PMC statuses changed significantly between September 27, 2007 and the end of the first annual review. Most notably, after the first review was completed, nearly half of all PMRs/PMCs that were categorized with an inaccurate status were re-classified as submitted. The percentage of pending PMRs/PMCs decreased from 64% to only 14%, but the PMRs/PMCs with submitted status increased from 14% to 36%.

During the course of the second annual review this status correction was not necessary, however the status of 591 PMRs/PMCs changed as a result of progressing through the PMR/PMC lifecycle or missing milestone dates. For those PMR/PMC statuses that were updated, nearly half (46%) were updated to fulfilled, reflecting a significant effort from the review divisions to complete reviews of the large number of submitted final reports identified during the first Backlog review. Only 7% of PMRs/PMCs that were on-schedule after the first annual review became delayed during the course of this review. After completing the second annual Backlog review, the largest segment of PMRs/PMCs were classified as fulfilled (31%), followed by submitted (24%), delayed (17%) and ongoing (10%). The large decrease in the percentage of submitted PMRs/PMCs can be attributed to FDA staff reviewing submitted final reports by sponsors and issuing fulfillment letters. However, the largest segment of open PMRs/PMCs is still awaiting FDA review of a sponsor-submitted final report.

Off-schedule PMRs and PMCs

PMRs/PMCs can be classified as either on-schedule or off-schedule, depending on their status category. On-schedule PMRs/PMCs are making progress toward completing the study or trial according to their assigned schedule and are classified as pending, ongoing or submitted. Off-schedule PMRs/PMCs are those that are not currently progressing according to the original schedule, and are therefore classified as either delayed or terminated. After this review, 86% (227/264) of the delayed PMRs/PMCs are off-schedule due to a missed final report milestone date while only 1% (3/264) are delayed because of missed study/clinical trial completion date. Out of the 227 PMRs/PMCs that were delayed due to a missed final report milestone date, more than half (53%) had studies/trials in progress. Therefore, even though the sponsor missed the final report milestone, which is the last milestone for a PMR or PMC, in most of these cases the sponsor was making an effort to satisfy the requirements of the PMR/PMC and it is reasonable to assume that the studies/trials remain feasible and will eventually be completed.

After completion of the second annual review, two-thirds (67%) of the PMRs/PMCs that were considered delayed in the first annual review remained delayed. As in the first annual review, the proportion of off-schedule PMRs/PMCs was similar across most of the review divisions. The review divisions with the most off-schedule PMRs/PMCs included the Divisions of Biologic Oncology Products, Anti-Viral Products, and Anesthesia, Analgesia, and Rheumatology Products.

Submitted PMRs/PMCs

Tracking and review is an important part of the PMR/PMC process, ensuring successful and timely completion of these requirements/commitments. A PMR/PMC is classified as submitted once FDA receives the final report. A majority of the status changes made during the first

annual review resulted in the status being updated to submitted. During this review, half of those identified as submitted in the first review retained the submitted status designation.

FDA's internal policy is to complete their review of PMR/PMC final report submissions within 12 months of receipt of the final report. Of the submitted Backlog PMRs/PMCs, three review divisions each had 50 or more reports to review, and most of them were identified as submitted before the first annual Backlog review. However, the review divisions made a significant effort since the first Backlog review to review final reports and issue fulfillment letters. The main reasons for failure to meet review goal dates were competing workload priorities and lack of experienced review staff.

PMRs/PMCs Lacking Final Report Milestone Dates

When establishing PMRs/PMCs, FDA generally 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 or 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. Of the Backlog PMRs/PMCs, there were 466 (30%) that had no specific completion date (i.e., final report submission date) associated with them, which allowed a significant number of requirements/commitments to remain 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, over half (62%) of the PMRs/PMCs without completion dates were created more than 10 years ago. Additionally, the FDA has either issued fulfillment or release letters for nearly half (44%) of the PMRs/PMCs without completion dates. These findings suggest that FDA has improved their PMR/PMC development policies across review divisions to include completion dates, and has made efforts to close out many of those PMRs/PMCs without completion dates in spite of the inherent tracking challenges.

Backlog PMR/PMC Recommendations

The main objective of conducting an annual Backlog review is to identify PMRs/PMCs for possible re-evaluation or closure (i.e., release or fulfill). During the course of the second annual review, Booz Allen contacted each review division to follow-up on each recommendation issued as a result of the first review and determined what action, if any, was taken by the division based on the recommendation.

In the first annual Backlog review, Booz Allen issued re-evaluate recommendations for 74 PMRs/PMCs, and approximately half (47%) resulted in action by the review division to discuss or close out the PMR/PMC. In the first annual review, a fulfill or release recommendation was issued to those PMRs/PMCs where documentation (i.e., review or memo) was discovered in the FDA data systems indicating that the PMR/PMC should be either fulfilled or released. Of the PMRs/PMCs that received a fulfill recommendation, 7 (35%) were issued fulfillment letters notifying the sponsor of closure of the PMR/PMC. The action taken on 39% of the PMRs/PMCs that received a release recommendation was issuance of a release letter.

During the second annual review, 913 (59%) of the 1551 PMRs/PMCs in the Backlog were reviewed and issued recommendations according to the prioritization scheme. The remaining PMRs/PMCs were not issued recommendations because they were either closed (i.e., fulfilled or released) or the correct status was unknown. For the purpose of priority determination, open PMRs/PMCs were categorized into three groups: off-schedule (18%), on-schedule with no final report submission date (8%), and on-schedule with a final report submission date (33%).

During this second annual review, Booz Allen recommended no change for 84% of the PMRs/PMCs in the off-schedule category. Of the on-schedule PMRs/PMCs with no final report submission dates, 61% 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 52% (33/63) off-schedule PMRs/PMCs and 48% (30/63) on-schedule PMRs/PMCs with no final report submission date. For the off-schedule PMRs/PMCs, 4% were recommended for release. Most of the PMRs/PMCs (72%) recommended for fulfill had been reviewed by FDA staff who had internally documented that the PMR/PMC should be fulfilled. More than three-quarters (77%) of the recommendations for release or re-evaluate are repeat recommendations from the first annual Backlog review that were not addressed by the review divisions. Most of the PMRs/PMCs recommended for re-evaluation and release were in the Divisions of Medical Imaging and Hematology Products (DMIHP) and Dermatology and Dental Products (DDDP). Many (44%) of PMRs/PMCs recommended for re-evaluation did not have final report submission dates and 54% 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 or trials 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 or 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 (Food and Drug Administration Amendments Act of 2007 (FDAAA), Title IX, Section 901)[2]

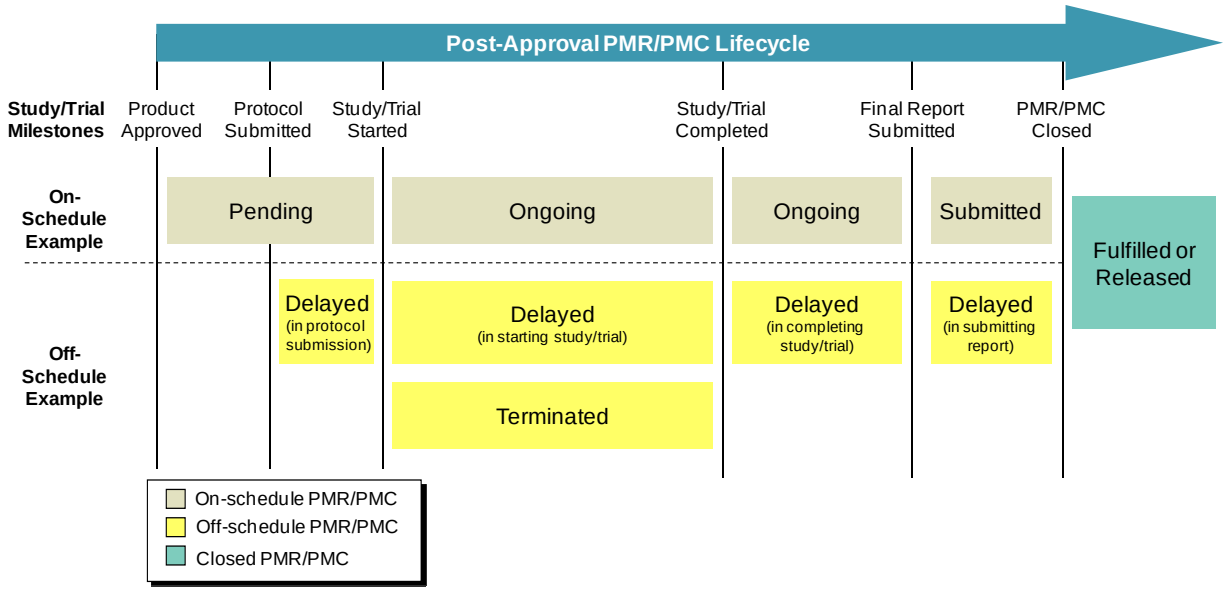
A PMC is a study or trial that a sponsor agrees in writing to conduct after approval of the product. PMCs are typically designed to gather additional information about product safety,

[2] Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 901, in Title IX of FDAAA, created a new section 505(o) 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)(1), 505(z), and 303(f) of the FDCA, 21 U.S.C. 355(o)(1), 355(z), and 333(f)).

efficacy, or optimal use, and FDA has determined through a carefully deliberated process that the information is not a condition of approval.

Each PMR/PMC is classified under one of the seven status categories[3] (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 schedule, while those that are off-schedule (i.e., delayed or terminated) have either missed one of their milestone dates or are not progressing.

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.[4] These annual status reports are to include the following elements:

- Description of the PMR/PMC
- Original timeline for achieving PMR/PMC milestones (i.e., final protocol submission, study/trial start, study/trial completion, and final report submission)
- A revised timeline for completing the PMR/PMC, if applicable[5]
- Current status of the PMR/PMC (i.e., pending, ongoing, submitted, delayed, terminated)
- Explanation of status

[3] These status categories were established and defined in 21 CFR 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8).
[4] This reporting requirement is specified in section 506B of the Federal Food, Drug, and Cosmetic Act (FDCA; 21 U.S.C. 356b)
[5] Although schedule revisions are sometimes necessary, FDA will use the original PMR/PMC schedule to determine the study/trial progress and to designate the PMR/PMC status as pending, ongoing, or delayed (21 CFR 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8)).

FDA is also required to track and monitor the progress of PMRs and PMCs to ensure they are completed in a timely manner. This aspect of pharmacovigilance is primarily accomplished by review of the protocols related to PMRs/PMCs, final reports and annual status reports submitted by the sponsor. FDA maintains a continuously-updated internal database of all PMRs/PMCs and their current statuses 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.

Last year, Booz Allen completed the first annual review of the Backlog of PMRs/PMCs to determine if any of the requirements/commitments should be revised or released.[6] After completion of this review, Booz Allen determined that the majority of the Backlog PMRs/PMCs were actually submitted, whereas the internal database indicated that most PMRs/PMCs were pending. Overall, of those PMRs/PMCs reviewed for the first Backlog review, 51% had an inaccurate status and required a status update. In order to meet requirements outlined in Section 921 of the FDAAA 2007, a second annual review was conducted to determine if any requirements/commitments should be revised or released. The legislation also requires FDA to report to Congress on these recommendations and to assign completion milestone dates for requirements/commitments without such dates.

2.1. Objectives and Scope

The goal of this task was to complete a second annual review all open PMRs and non-CMC[7] 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 lack completion dates
- Analyze PMRs/PMCs that are recommended for closure/re-evaluation to determine why the studies or clinical trials may be no longer necessary or feasible

For the first annual review, FDA provided a list of 1643 open PMRs and PMCs derived from the internal PMR/PMC tracking systems on September 27, 2007. After the first annual Backlog review, which was completed on April 10, 2009,[8] Booz Allen determined that the actual Backlog cohort consisted of 1531 open PMRs and PMCs.[9] During the course of the second annual review, Booz Allen discovered additional PMRs/PMCs that were erroneously included in or excluded from this group. PMRs/PMCs that were inaccurately included were removed for the following reasons:

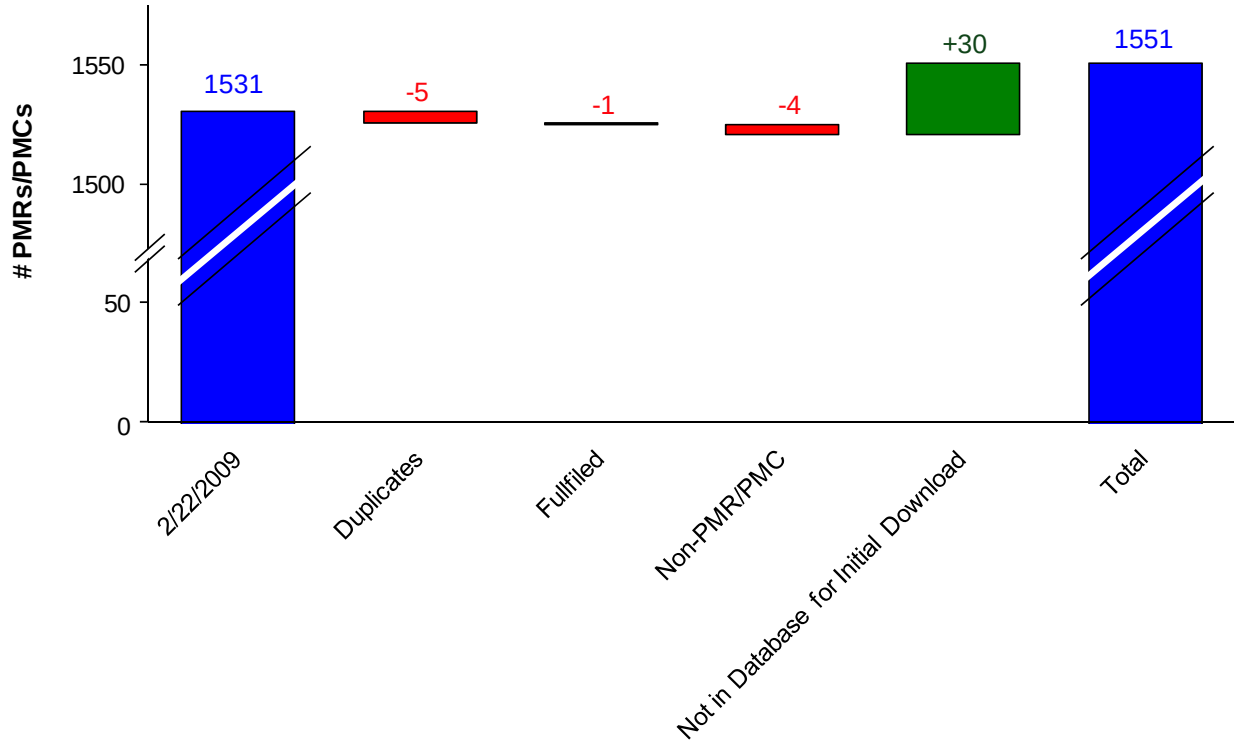
[6] Independent Evaluation of FDA's Prescription Drug User Fee Act – Evaluations and Initiatives; CDER Technical Support and Analysis. Booz Allen Hamilton (April 2009).
[7] CMC PMCs are not required to report under section 506B of FDCA and are not included in the PMC Backlog.
[8] The data for the April 10, 2009 report was locked on February 22, 2009.
[9] Independent Evaluation of FDA's Prescription Drug User Fee Act – Evaluations and Initiatives; CDER Technical Support and Analysis. Booz Allen Hamilton (April 2009).

- The PMR/PMC was a duplicate[10] of another PMR/PMC in the Backlog
- The PMR/PMC had already been fulfilled
- The requested information did not qualify as a PMR or PMC

PMRs/PMCs that were subsequently added to the Backlog had been excluded because the requirement or commitment was not entered into the PMR/PMC database at the time of initial download of data for the report completed April 10, 2009.

After accounting for these issues, the actual PMR/PMC Backlog as of September 27, 2007, consisted of 1551 open PMRs/PMCs (Exhibit 2).

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



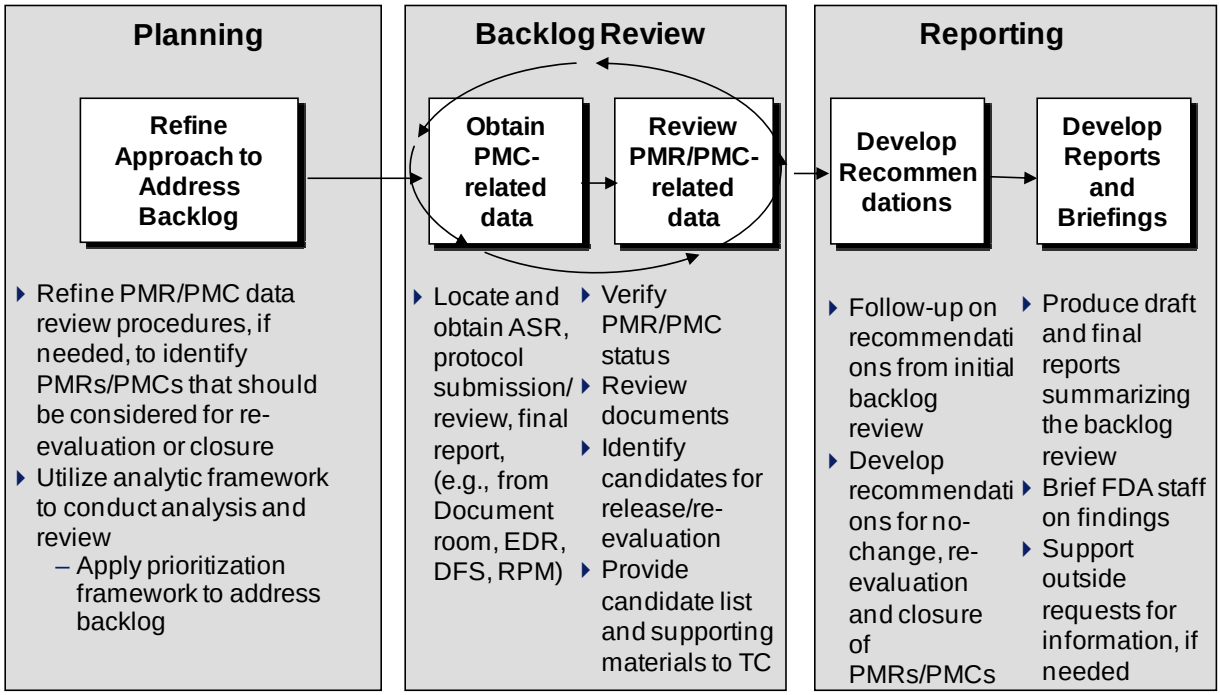
Adjustments to PMR/PMC Backlog Composition

[10] 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. For example the NDAs 21266 and 21267 were reviewed together and shared a single action letter with 4 PMCs.

3. METHODOLOGY

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

Exhibit 3: Technical Approach for Backlog Review



During the planning phase for the second annual Backlog review, the approach and standard processes for data gathering and review employed in the previous review were refined to ensure completeness and consistency. The framework utilized during the first annual review was used again to prioritize Backlog PMRs/PMCs for review for recommendations for closure or re-evaluation, based largely on PMR/PMC status (see Appendix A). The second annual Backlog review was initiated by determining the accurate status for all PMRs/PMCs in the Backlog, since the prioritization scheme for the Backlog review was dependent on accurate status classification. This was accomplished by first comparing the status of the PMR/PMC listed in the internal PMR/PMC database 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 reports
- FDA-sponsor communications (e.g., meeting minutes, fulfillment letters, release letters)
- Internal FDA memos and reviews (e.g., discipline review of final report)

Statuses were also updated throughout the course of the review through the review of incoming annual status reports. 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 once again 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 previously developed and validated by the TAG for the first annual review. Recommendations will be reported to the review division's Tracking Coordinators who will work with the review teams to accept or revise the recommendations. PMRs/PMCs lacking completion dates were also identified and will also be reported to the review division to work with the sponsor to establish dates.

During this second annual review, review divisions were contacted to determine whether any action or discussion took place based on the re-evaluate, release and fulfill recommendations made for individual PMRs/PMCs in the first annual review. Additionally, FDA data systems were examined to find any correspondence from FDA to sponsors that established completion dates for those PMRs/PMCs that did not have completion dates when they were issued. This information was compiled and analyzed to determine what steps FDA took to address the recommendations made in the first annual review report.

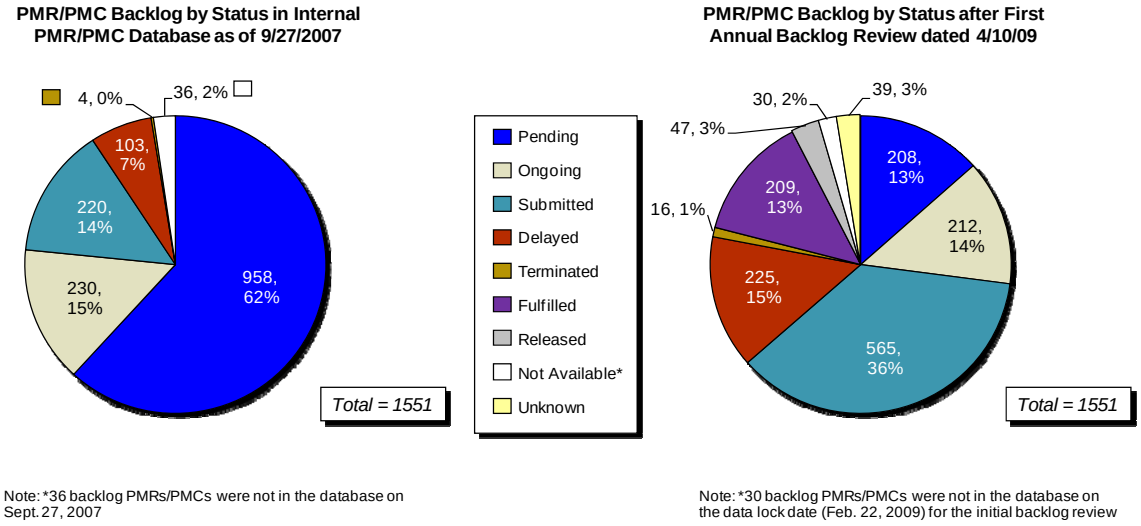
4. FINDINGS

The key findings are presented in the following sections from the second annual 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 review.

4.1. PMR/PMC Backlog Characterization

The cohort defined as the PMR/PMC Backlog that was evaluated for this task included 1253 New Drug Application (NDA) PMRs/PMCs and 298 Biologic License Application (BLA) PMRs/PMCs within CDER that were open as of September 27, 2007. The distribution of Backlog PMR/PMC statuses changed significantly between September 27, 2007 and the completion of the first annual Backlog review. On the date FDAAA was enacted, most Backlog PMRs/PMCs were categorized as pending (62%), followed by ongoing (15%) and submitted (14%) (Exhibit 4). After reviewing and updating the status for the PMRs/PMCs, the largest segment of Backlog PMRs/PMCs was accurately categorized as submitted (36%), followed by delayed (15%), ongoing (14%) and pending (13%). The percentage of pending PMRs/PMCs decreased from 62% to only 13%, 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 aggregate status represents the starting point for the second Backlog review.

Exhibit 4: PMR/PMC Backlog by Status in Internal PMR/PMC Database as of 9/27/2007 and after First Annual Backlog Review

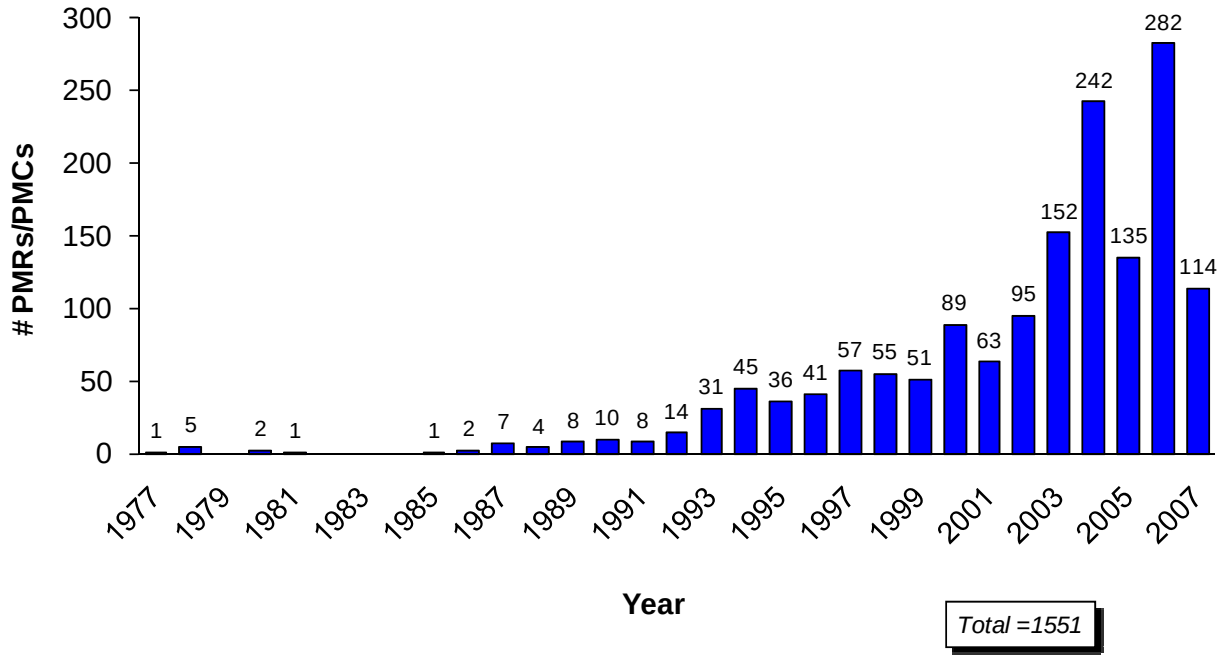


Note: *36 backlog PMRs/PMCs were not in the database on Sept. 27, 2007

Note: *30 backlog PMRs/PMCs were not in the database on the data lock date (Feb. 22, 2009) for the initial backlog review

Approximately half (773 of 1551) of the Backlog PMRs/PMCs were created between 2004 and 2007 (Exhibit 5).

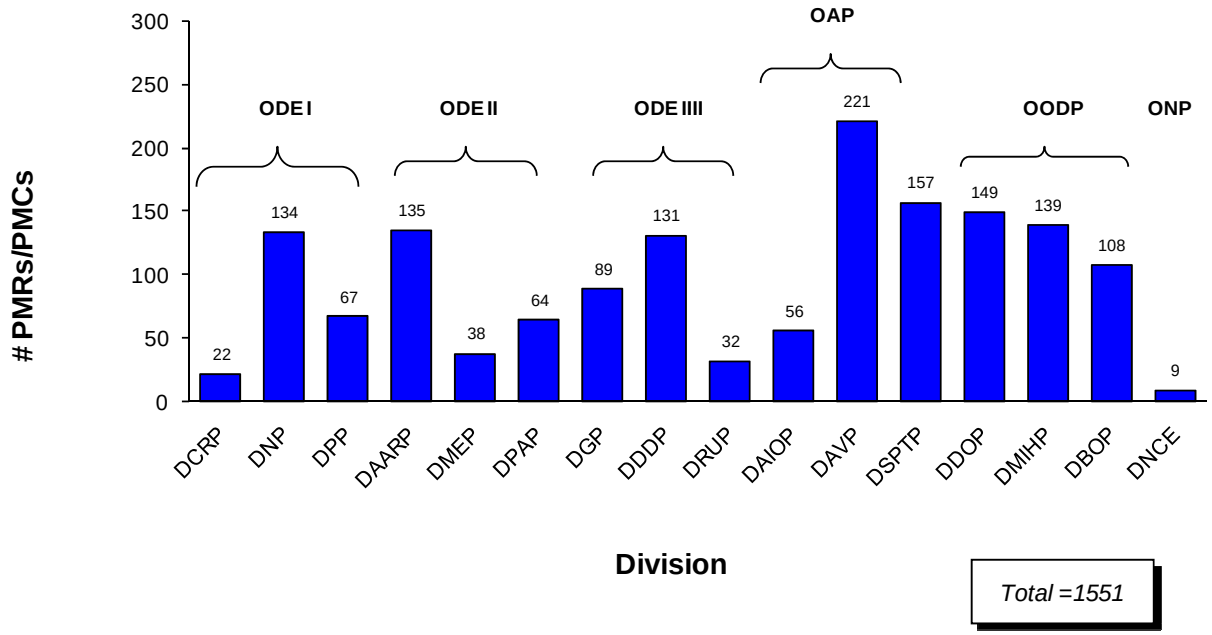
Exhibit 5: PMR/PMC Backlog by Year Established



The number of Backlog PMRs/PMCs varied considerably across review divisions (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 evaluation, 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.[11]

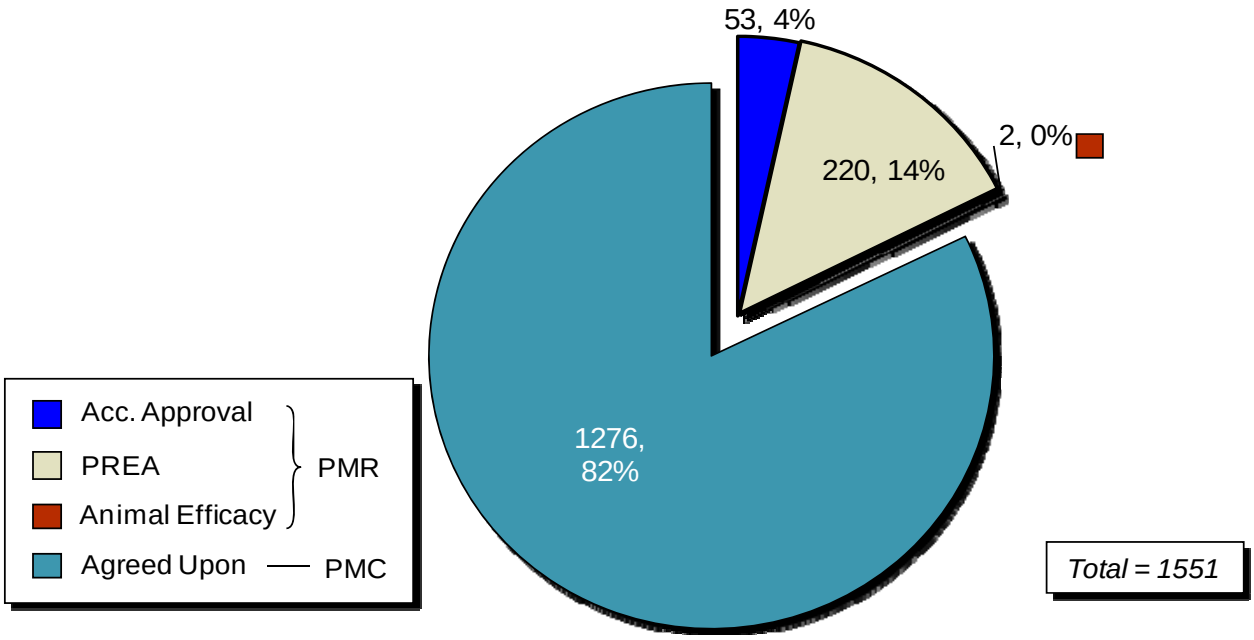
Exhibit 6: PMR/PMC Backlog by Review Division



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

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 4% of the PMRs/PMCs in the Backlog were established under the Accelerated Approval provision (Exhibit 7).

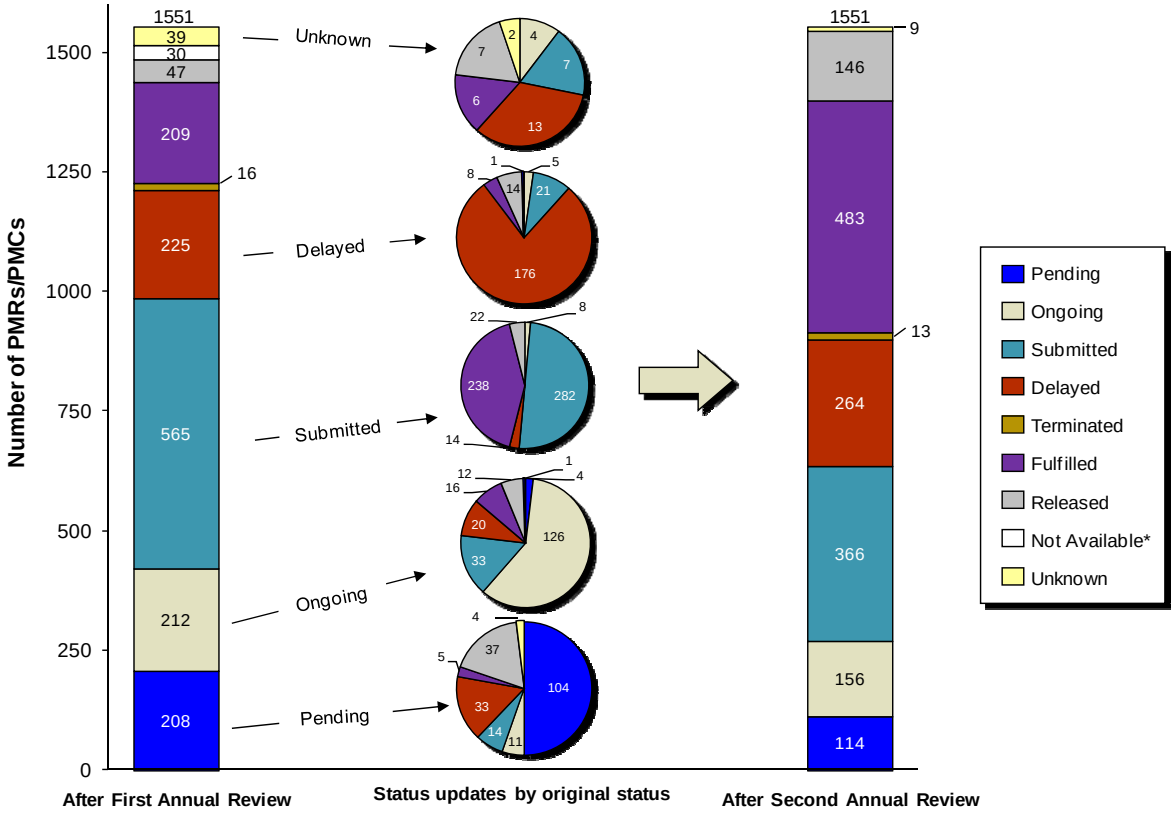
Exhibit 7: PMR/PMC Backlog by Type



4.2. Status Progression Between Reviews

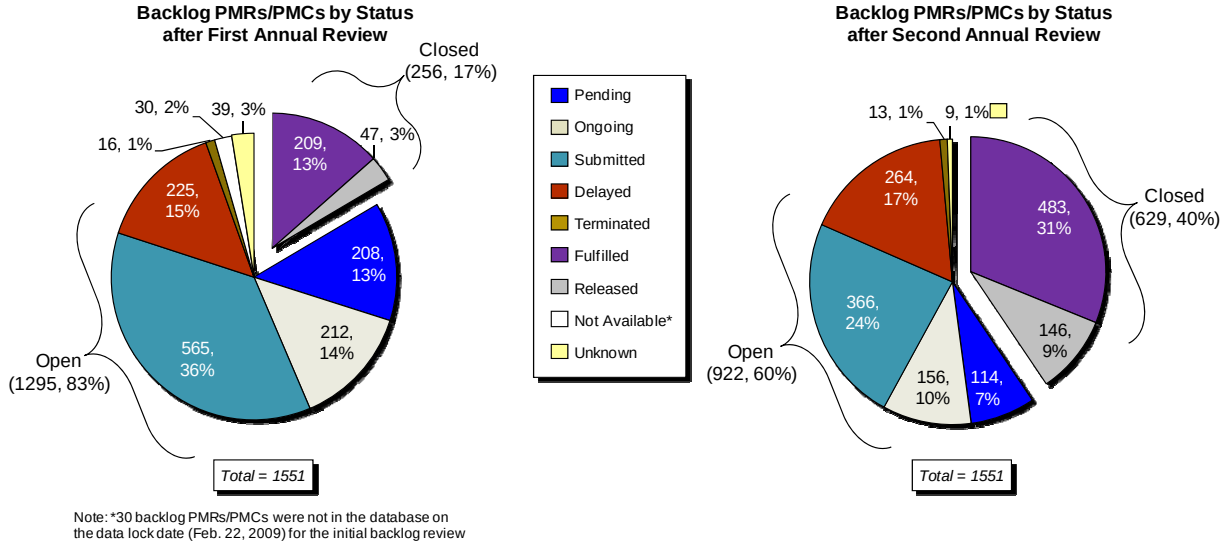
During the course of the second annual review, the status of 591 PMRs/PMCs changed as a result of progressing through the PMR/PMC lifecycle (Exhibit 8) or missing milestone dates. In examining the PMRs/PMCs whose statuses required updates, 273 (46%) were categorized as fulfilled after this review. Of the 212 PMRs/PMCs that were determined to be ongoing after the first annual review, 33 (16%) were updated to submitted and 20 (9%) were updated to delayed. The majority (33%) of PMRs/PMCs that were classified as unknown after the first annual review were updated to delayed during this review. After the second annual review, more than three-quarters (78%, 176/225) of the PMRs/PMCs identified as delayed in the first annual review remained delayed. Only 7% of PMRs/PMCs that were on-schedule after the first annual review became delayed during the course of this review.

Exhibit 8: PMR/PMC Backlog Status Progression after Second Annual Review



The overall distribution of Backlog PMR/PMC statuses changed significantly between the first annual Backlog review and the second annual Backlog review. After the first annual review, the largest segment of Backlog PMRs/PMCs was submitted (36%), followed by delayed (15%) and ongoing (14%) (Exhibit 9). After completing the second annual review and updating the status for relevant PMRs/PMCs, Booz Allen determined that the largest segment of Backlog PMRs/PMCs are accurately categorized as fulfilled (31%), followed by submitted (24%) and delayed (17%). After completion of this review, the percentage of fulfilled PMRs/PMCs increased from 13% to 31% and the percentage of released PMRs/PMCs increased from 3% to 9%. There was a considerable decrease in the percentage of submitted PMRs/PMCs from 36% to 24%, which can be attributed to FDA staff reviewing submitted final report by sponsors and issuing fulfillment letters. However, the largest segment of open PMRs/PMCs is still awaiting FDA review of a sponsor-submitted final report.

Exhibit 9: Comparison of Overall Backlog PMR/PMC Status



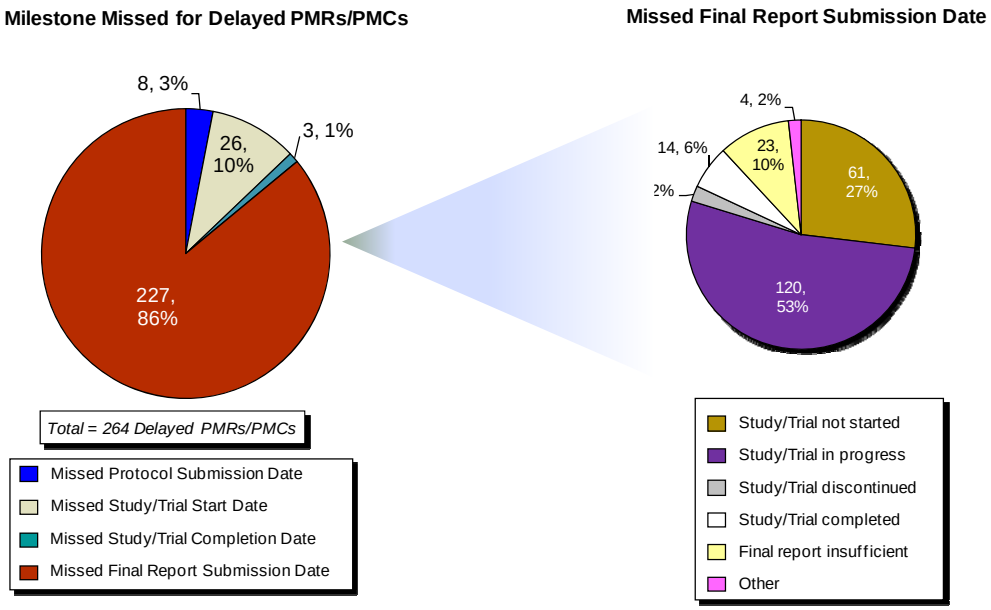
Note: *30 backlog PMRs/PMCs were not in the database on the data lock date (Feb. 22, 2009) for the initial backlog review

4.3. Off-Schedule PMRs and PMCs

Off-schedule PMRs/PMCs are those that are not currently progressing according to the original 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 report was the cause of 86% of delayed PMRs/PMCs while only 1% were delayed due to the study/trial completion milestone date (Exhibit 10). 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.[12] Out of the 227 PMRs/PMCs that were delayed due to a missed final report milestone date, more than half (53%) had studies/trials in progress. Therefore, even though the sponsor missed the final report milestone, which is the last milestone for a requirement/commitment, in most of these cases the sponsor was making an effort to satisfy the requirements of the PMR/PMC and it is reasonable to assume that the studies/trials remain feasible and will eventually be completed.

[12] Out of 1551 Backlog PMRs/PMCs, 221 have study/trial completion dates, and 1085 have final report dates.

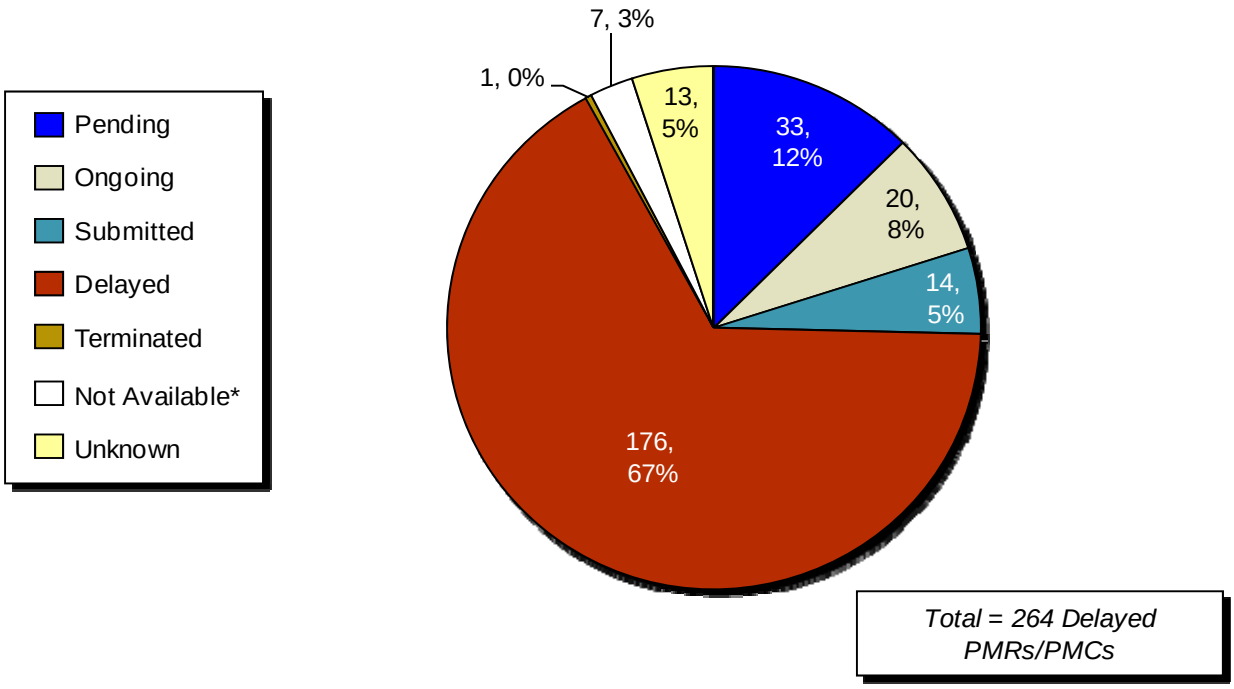
Exhibit 10: Evaluation of Progress for PMRs/PMCs with Delayed Status



Note: "Other" includes one PMR/PMC that had alternative data submitted, two PMRs/PMCs for which the sponsor was requested to submit supplements that were not received, and one PMR/PMC that was converted into a REMS.

Two-thirds (67%, 176/264) of the PMRs/PMCs that are delayed after this review were delayed after completion of the first annual review (Exhibit 11). Of those currently delayed PMRs/PMCs that were pending after the first annual review, 55% (18/33) became delayed by missing the final report milestone date. Most (94%) of the PMRs/PMCs whose status went from pending to delayed only had a final report submission date and no other milestone dates. This finding illustrates the difficulty of accurately tracking and representing PMR/PMC status throughout its lifecycle if standard milestone dates are missing.

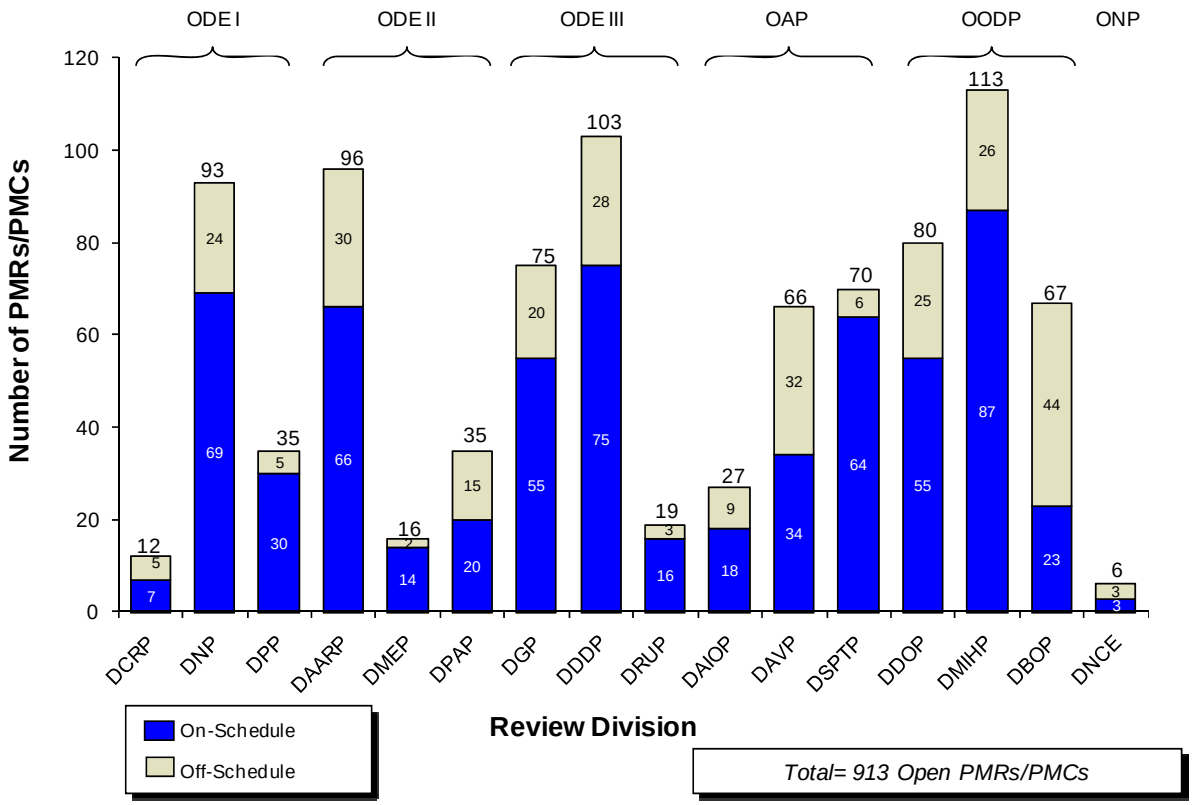
Exhibit 11: Currently Delayed PMRs/PMCs by Status in First Annual Backlog Review



Off-schedule PMRs/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),[13] Anti-Viral Products (DAVP), and Anesthesia, Analgesia, and Rheumatology Products (DAARP) (Exhibit 12).

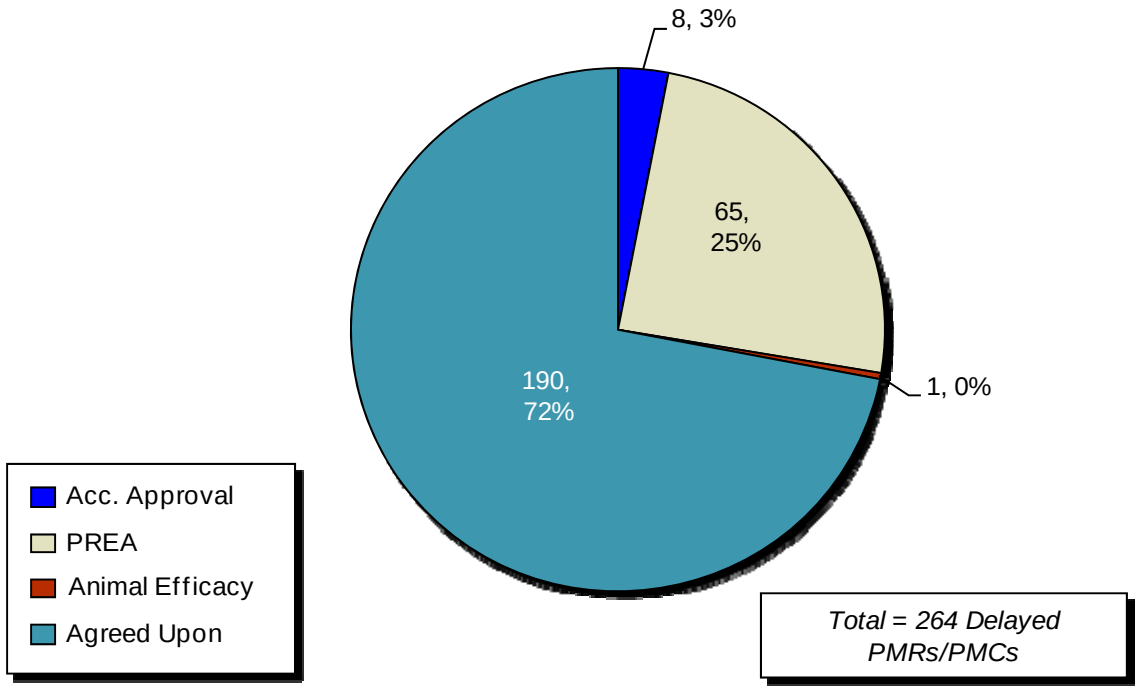
[13] DBOP typically keeps a PMR/PMC classified as delayed if a final report was submitted but deemed insufficient to fulfill the PMR/PMC. This PMR/PMC remains open until alternative results are accepted by DBOP. This practice contributes to the higher proportion of off-schedule PMRs/PMCs compared to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

Exhibit 12: On- and Off-Schedule PMRs/PMCs by Review Division



Most delayed studies/trials were agreed-upon PMCs (72%) (Exhibit 13). Only 3% of delayed PMRs/PMCs were PMRs/PMCs associated with products that received accelerated approval designation. In the overall Backlog (1551 PMRs/PMCs), 14% were PREA studies (Exhibit 7), while among delayed PMRs/PMCs, 25% were PREA PMRs. This PMR/PMC type distribution is similar to that of the overall cohort (Exhibit 7).

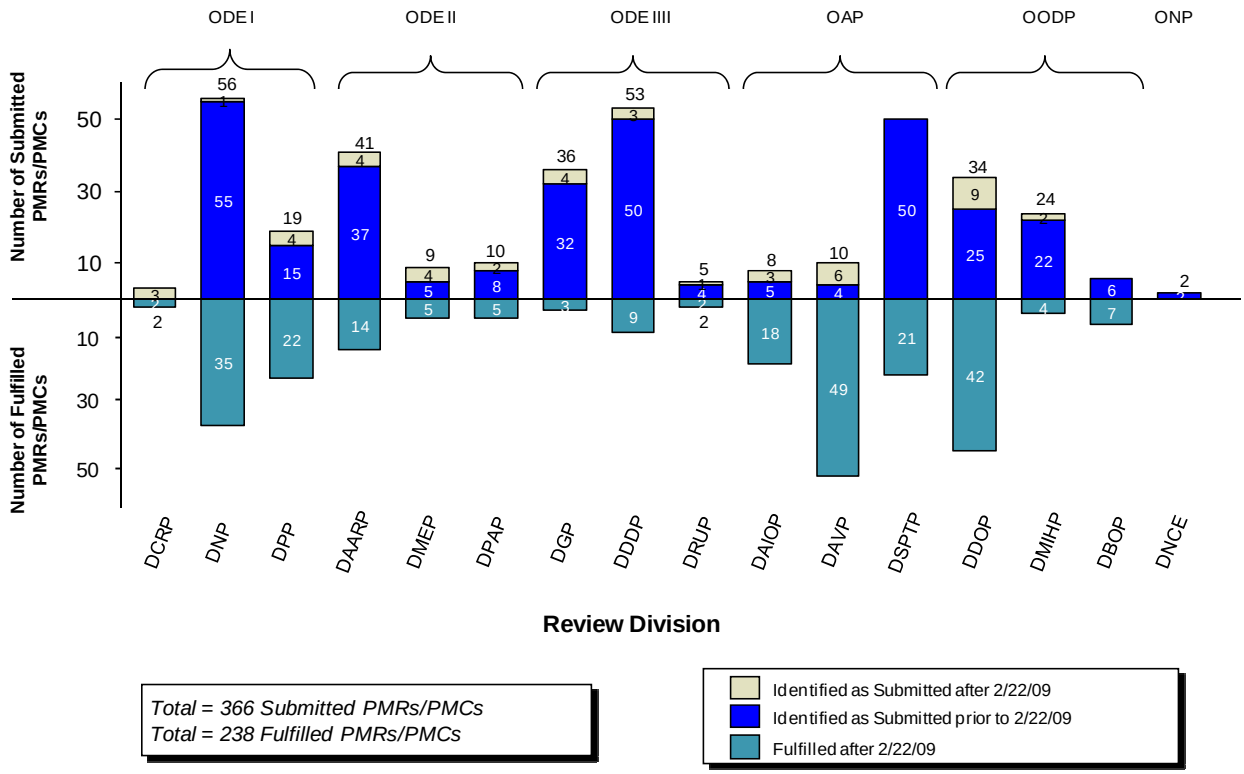
Exhibit 13: Delayed PMRs/PMCs by Type



4.4. Submitted PMRs/PMCs

As discussed in section 4.2, many of the PMRs/PMCs with status changes were updated to submitted after the first annual review and half of the PMRs/PMCs identified as submitted retained the status designation after this review. Of the submitted PMRs/PMCs, the Divisions of Neurology Products (DNP), Dermatology and Dental Products (DDDP) and Special Pathogen and Transplant Products (DSPTP) had the greatest numbers (56, 53 and 50, respectively) of reports to review, and most of them were identified as submitted before the first annual Backlog review (Exhibit 14). The Divisions of Drug Oncology Products (DDOP) and Anti-Viral Products (DAVP) had the greatest numbers of newly-identified submitted PMRs/PMCs. However, the review divisions made a significant effort since the first Backlog review to review final reports and issue fulfillment letters. The Divisions of Anti-Viral Products, Drug Oncology Products and Neurology Products issued the highest number of fulfillment letters (49, 42, and 35 respectively) compared to other divisions. This high rate of fulfillment reflects OND's commitment to reducing the number of Backlog PMRs/PMCs.

Exhibit 14: Status of Final Reports by Division

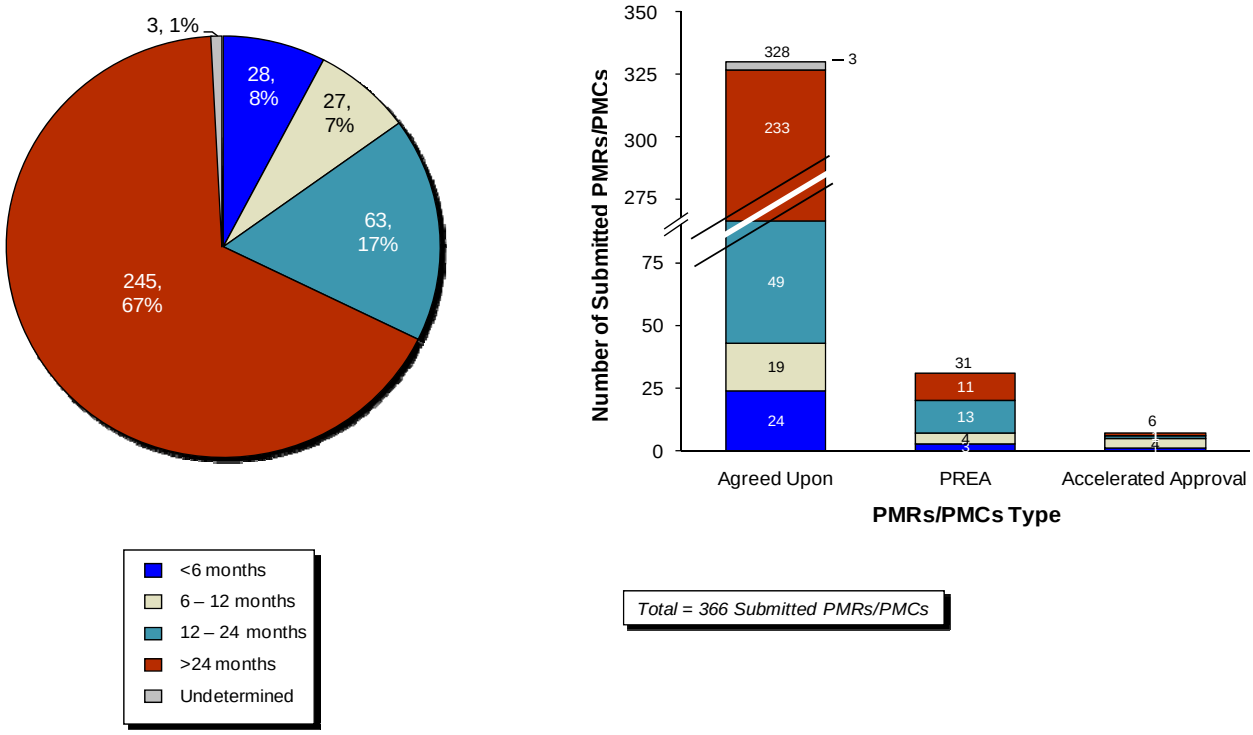


FDA's internal goal for completing review of PMR/PMC final reports is 12 months, except in cases where the final report was submitted as part of a submission that must adhere to PDUFA goal dates.[14] Final reports for 84% of the PMRs/PMCs classified as submitted were received more than 12 months ago and 67% of the PMRs/PMCs classified as submitted were received more than 24 months ago (Exhibit 15). Even though the FDA has experienced a significant increase in review staff in the past couple of years,[15] these newly hired reviewers may need more time to gain experience in conducting reviews and learning FDA's business processes before taking on a heavier workload sustained by a more seasoned reviewer. Therefore, there may be a lag in the time between the surge of newly hired review staff and the realization of a significant decrease in the number of older, pending final report submissions requiring review.

[14] The review timeframe for final 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 or ten months.

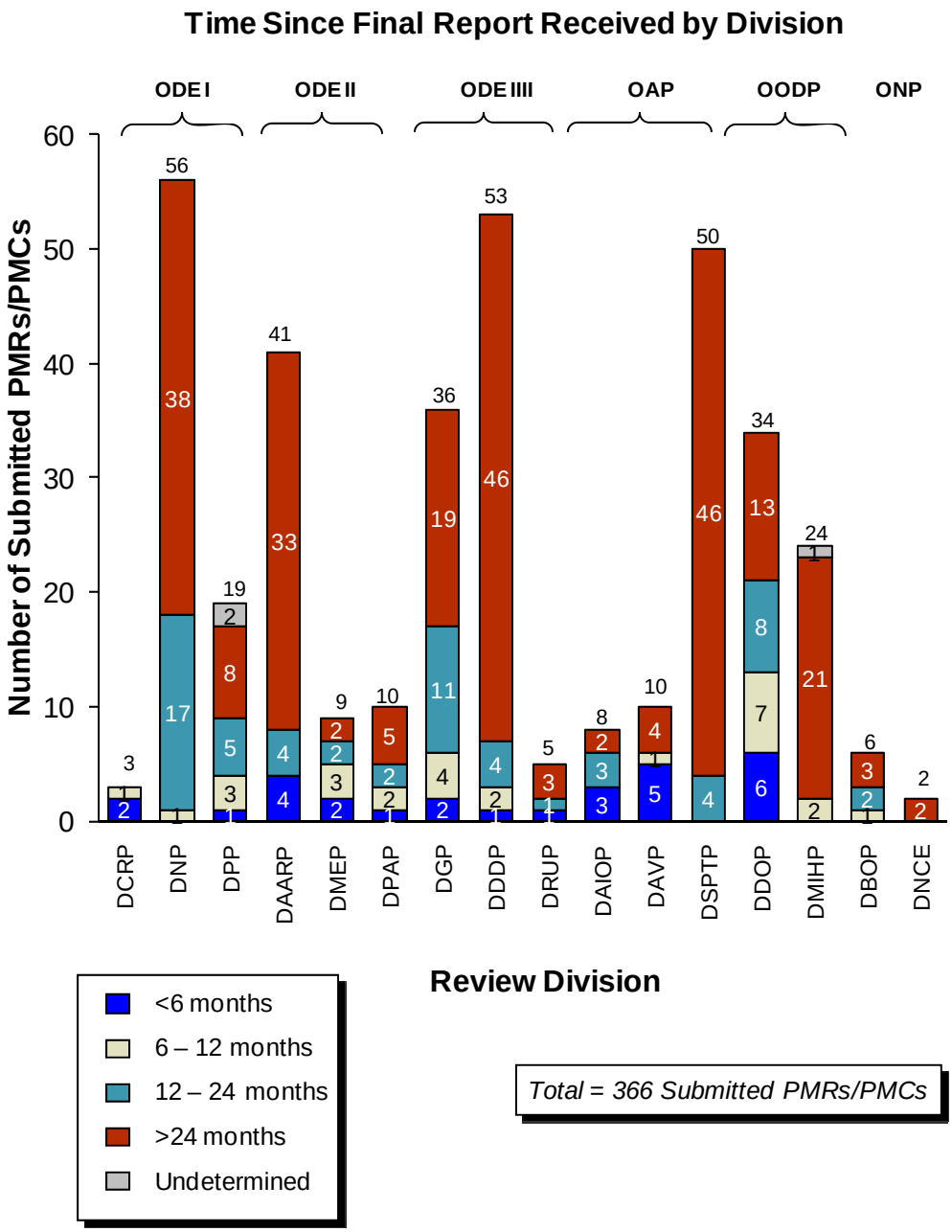
[15] "Reinforcements at Last: CDER Hiring Process Well Underway", The RPM Report, Vol.31, No. 12, Rawson, K. (2008)

Exhibit 15: Time since Final Report Received



Consistent with the overall quantity of PMR/PMC final reports to be reviewed by Divisions of Dermatology and Dental Products, Special Pathogen and Transplant Products and Neurology Products, these divisions also have the largest number of final reports received more than 24 months ago. There were 55 PMR/PMC final reports in the Division of Neurology Products that were received more than 12 months ago. In addition, all of the submitted PMRs/PMCs (i.e., 50 final reports) in the Division of Special Pathogen and Transplant Products (DSPTP) were received more than 12 months ago (Exhibit 16). Interestingly, out of the 47 PMRs/PMCs that have been fulfilled in DSPTP, 55% had no final report milestone dates and 85% (22/26) were fulfilled within the past 12 months.

Exhibit 16: Time since Final Report Received by Division



4.5. PMRs/PMCs Lacking Final Report Milestone Date

In developing PMRs/PMCs, FDA often communicates with sponsors to identify specific milestone dates that should be established and are subsequently used to track the progress of the requirement/commitment and determine its status. In the Backlog, there were 466 requirements/commitments that had no specific completion date or deadline associated with them. 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 was agreed-upon PMCs, which comprised of 96% (407/426) of the no-date/relative date requirements/commitments (Exhibit 17). 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, and there is not currently a consistent way to track and calculate these dates in FDA's tracking system.

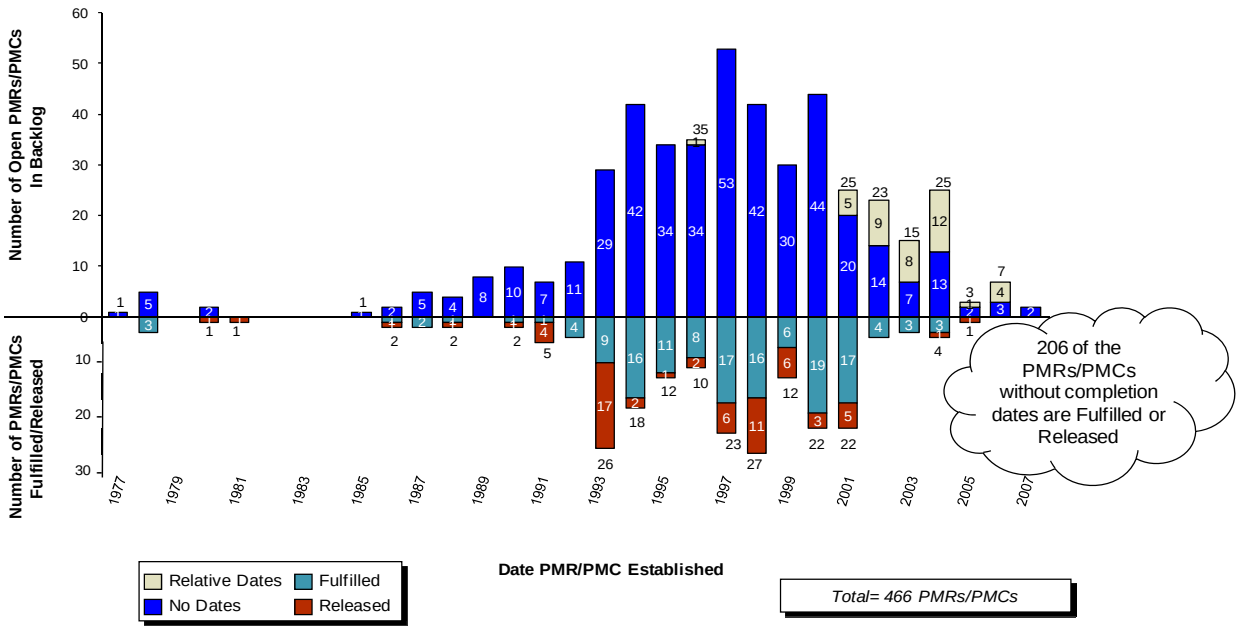
Exhibit 17: **PMRs/PMCs Lacking a Specific Completion Date**

	Relative Dates	No Dates
Accelerated Approval	2	12
PREA	1	6
Animal Efficacy	0	1
Agreed Upon	37	407
TOTAL	**40**	**426**

Over half (62%) of PMRs/PMCs without completion dates were created more than 10 years ago (Exhibit 18). 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). Exhibit 5). The decrease in the number of PMRs/PMCs missing a completion milestone date suggests that FDA has improved their practices based on experience and wider adoption of PMR/PMC development policies. Additionally, the FDA has either issued fulfillment or release letters for nearly half (44%) of the PMRs/PMCs without completion dates.

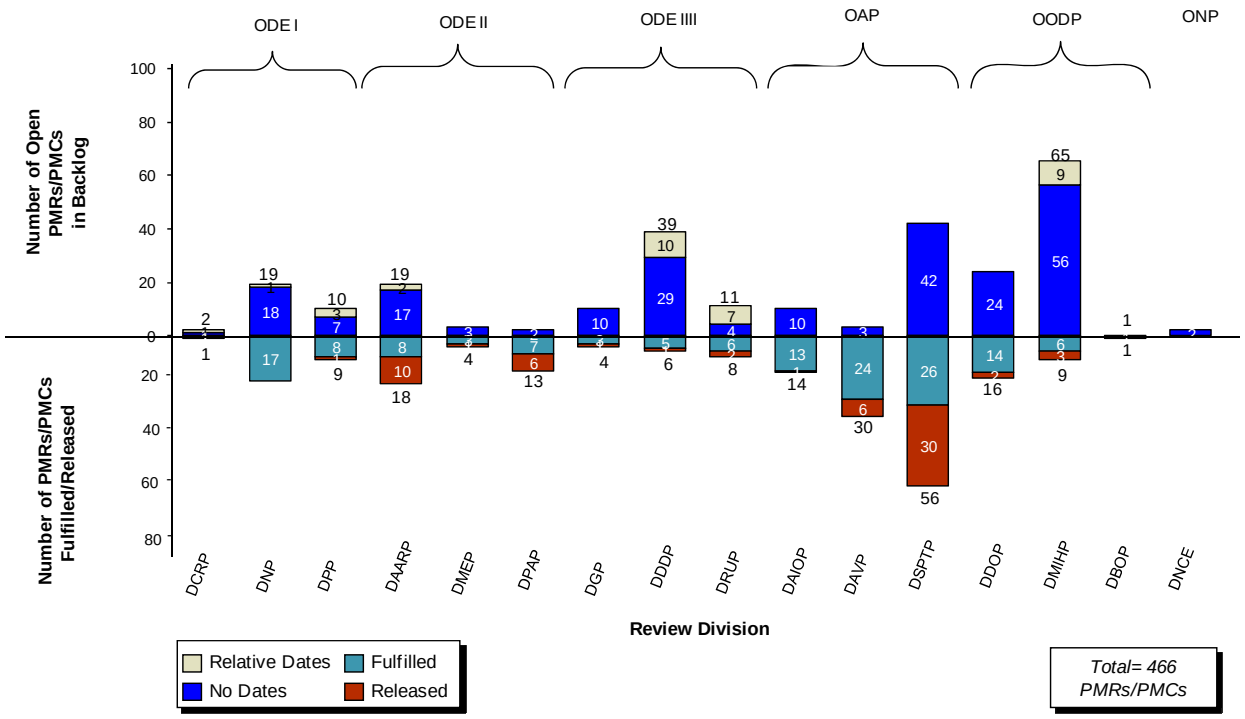
[16] Relative dates are not exact specified dates, but timelines for study/trial milestones based on completion of a previous milestone, e.g. 6 months after study/trial start date.

Exhibit 18: **PMRs/PMCs with No Completion Date or Relative Completion Date by Year Established**



Two review divisions, the Division of Special Pathogen and Transplant Products and the Division of Medical Imaging and Hematology Products, had a substantially greater number of PMRs/PMCs without specific completion dates than other review divisions (Exhibit 19). Notably, the Division of Special Pathogen and Transplant Products has issued fulfillment or release letters for more than half (57%) of its PMRs/PMCs without completion dates.

Exhibit 19: No Date PMRs/PMCs by Review Division

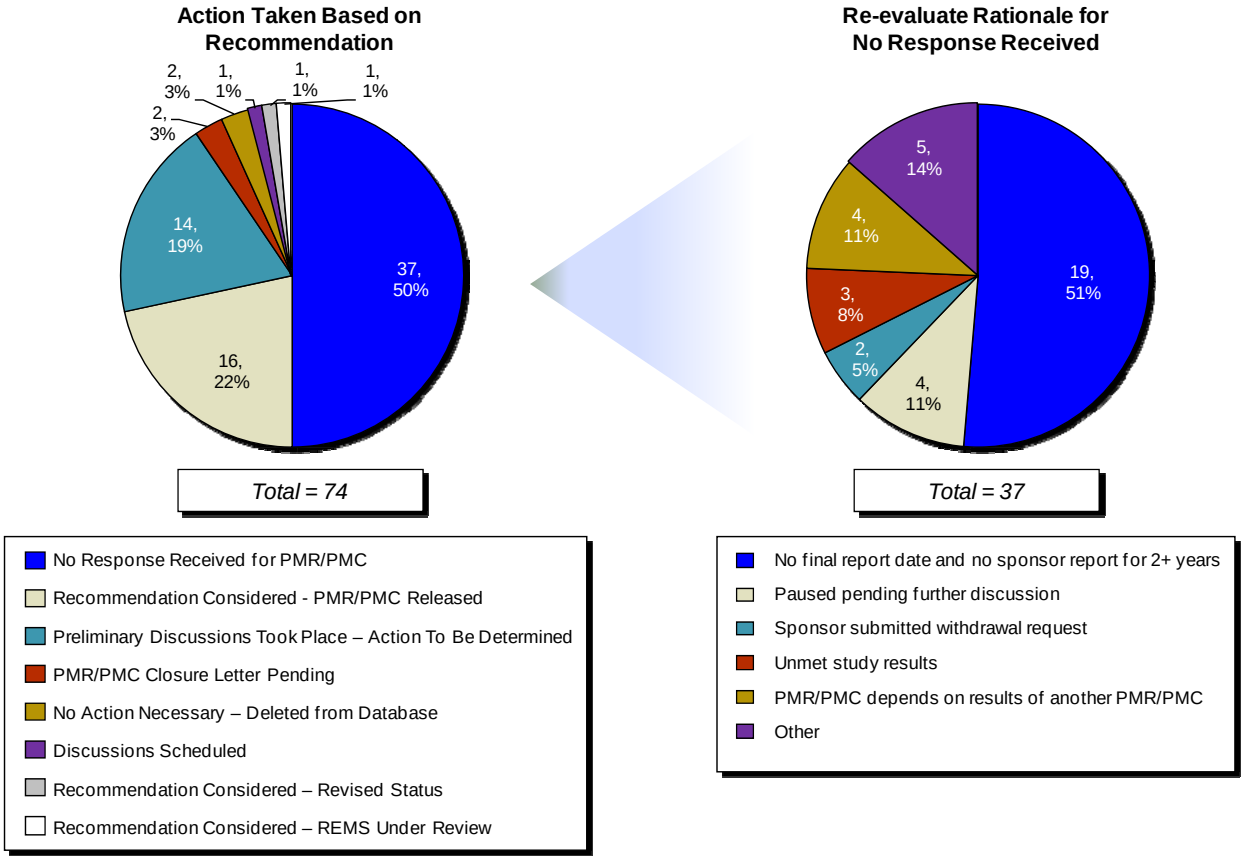


4.6. Backlog PMR/PMC Recommendations

The main objective of conducting an annual Backlog review is to identify PMRs/PMCs for possible re-evaluation or closure (i.e., release or fulfill). During the course of the second annual review, Booz Allen contacted each review division to follow-up on each recommendation issues in the first annual review to determine what action, if any, was taken by the division based on the recommendation.

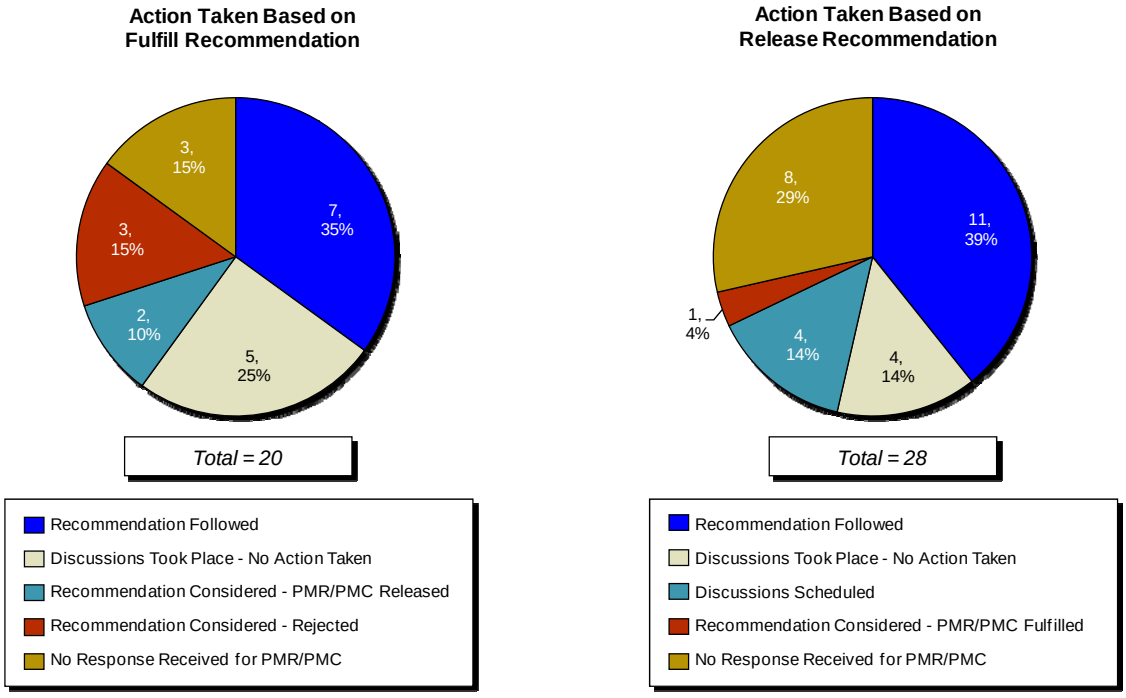
For the 115 PMRs/PMCs that received a recommendation to establish a completion date after the first annual review because a final report submission milestone was never established, none of the divisions issued a letter to the sponsors requesting or issuing a completion date. In the first annual Backlog review, Booz Allen issued re-evaluate recommendations for 74 PMRs/PMCs. Among these PMRs/PMCs, 25% were either released or scheduled for release, and 20% have either held discussion or scheduled discussion to determine whether the PMR/PMC should remain open or closed out (Exhibit 20). The distribution of the rationale for those re-evaluate recommendations where the review division did not provide a response on the action taken for the recommendation was similar to the distribution of the overall re-evaluation recommendation cohort from the first annual review.

Exhibit 20: Follow-up for Re-evaluate Recommendations Issued after First Annual Backlog Review



A fulfill or release recommendation was only issued to those PMRs/PMCs where evidence (e.g., internal review or memo) was found that a member of the review staff declared that a PMR/PMC should either be fulfilled or released. Of the PMRs/PMCs that received a fulfill recommendation, 7 (35%) were issued fulfillment letters notifying the sponsor of closure of the PMR/PMC (Exhibit 21). For those PMRs/PMCs where the recommendation was considered but rejected, the review division noted that the sponsor still had more to do before the PMR/PMC could be fulfilled. The action taken on 39% of the PMRs/PMCs that received a release recommendation was issuance of a release letter.

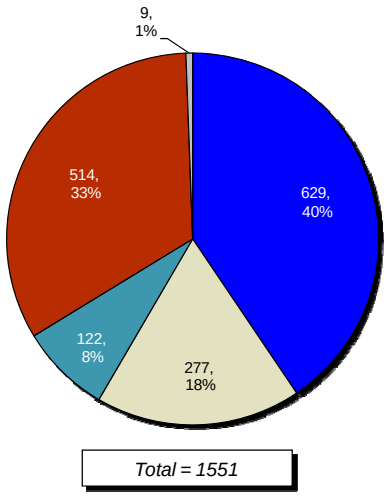
Exhibit 21: Follow-up for Fulfill/Release Recommendations Issued after First Annual Backlog Review



During the second annual review, 913 (59%) of the 1551 PMRs/PMCs in the Backlog were reviewed and issued recommendations according to the prioritization scheme described in Appendix A (Exhibit 22). The remaining PMRs/PMCs were not issued recommendations because they were either closed (i.e., fulfilled or released) or the correct status was unknown.[17]

[17] A PMR/PMC status was unknown 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 22: Backlog PMRs/PMCs by Prioritization for Review

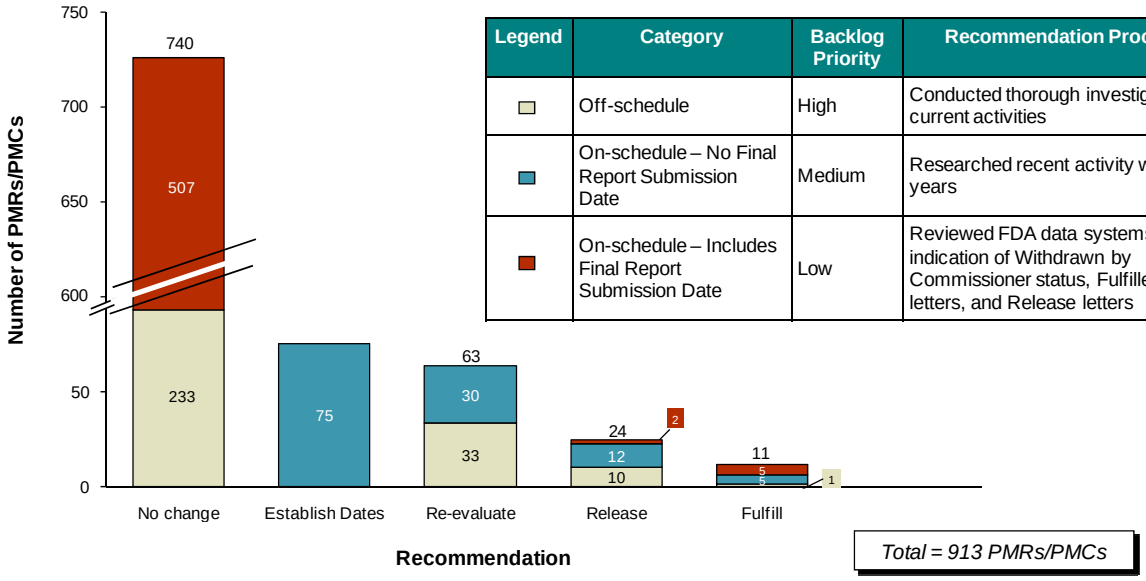


Legend	Category	Priority	Recommendation Process
	Off-schedule	High	Conducted thorough investigation of current activities
	On-schedule – No Final Report Submission Date	Medium	Researched recent activity within 2 years
	On-schedule – Existing Final Report Submission Date	Low	Reviewed FDA data systems 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 schedule, off-schedule but still in progress toward completion, or off-schedule but still relevant and feasible to conduct. Of the 913 PMRs/PMCs evaluated for recommendations, the vast majority (81%, 740/913) of Backlog PMRs/PMCs were recommended for no change. Only 63 (7%) 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 23).

For those PMRs/PMCs that were off-schedule, Booz Allen recommended no change for 84% (233/277) of them (Exhibit 23). Of the on-schedule PMRs/PMCs that lacked a final report submission milestone date, 61% (75/122) were issued a recommendation to proceed with the study or 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 52% (33/63) off-schedule PMRs/PMCs and 48% (30/63) on-schedule PMRs/PMCs with no final report submission date. Of the PMRs/PMCs recommended for release, 42% (10/24) were categorized as off-schedule.

Exhibit 23: Backlog PMR/PMC Recommendations by Prioritization

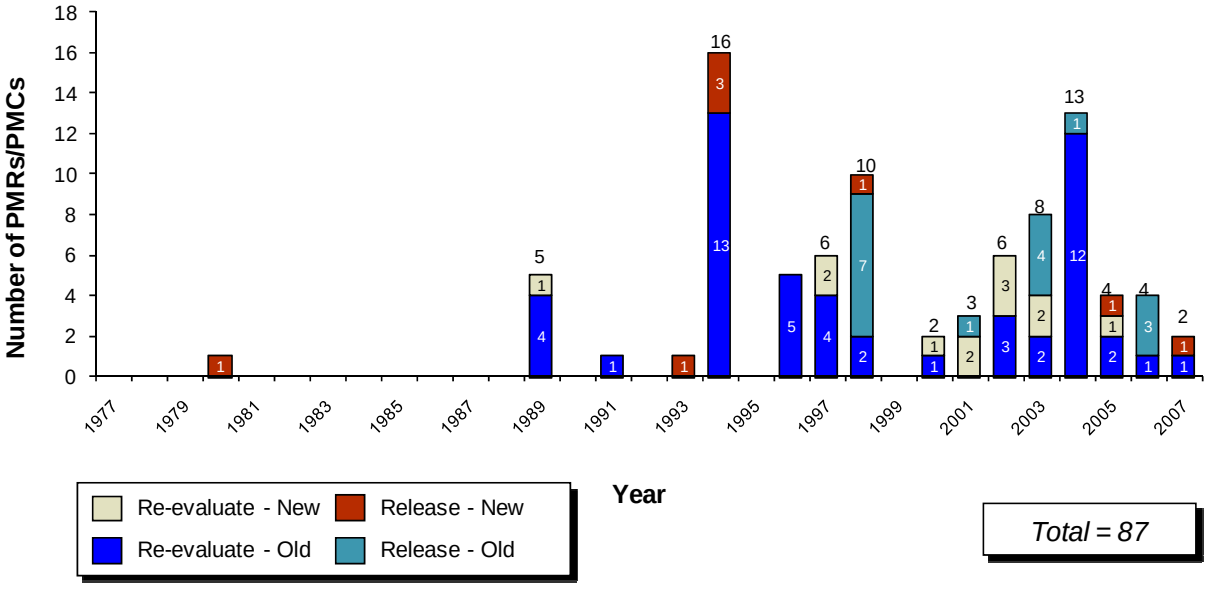


Legend	Category	Backlog Priority	Recommendation Process
	Off-schedule	High	Conducted thorough investigation of current activities
	On-schedule – No Final Report Submission Date	Medium	Researched recent activity within 2 years
	On-schedule – Includes Final Report Submission Date	Low	Reviewed FDA data systems for indication of Withdrawn by Commissioner status, Fulfilled letters, and Release letters

Note: No recommendations were made for 629 closed PMRs/PMCs (i.e., fulfilled or released) or 9 PMRs/PMCs for which the status was unknown.

PMRs/PMCs recommended for release did not exhibit an age-related trend (Exhibit 24). Over three-quarters (77%) (67/87) of the recommendations for release or re-evaluate are repeat recommendations (i.e., Old) from the first annual Backlog review that were not addressed by the review divisions.

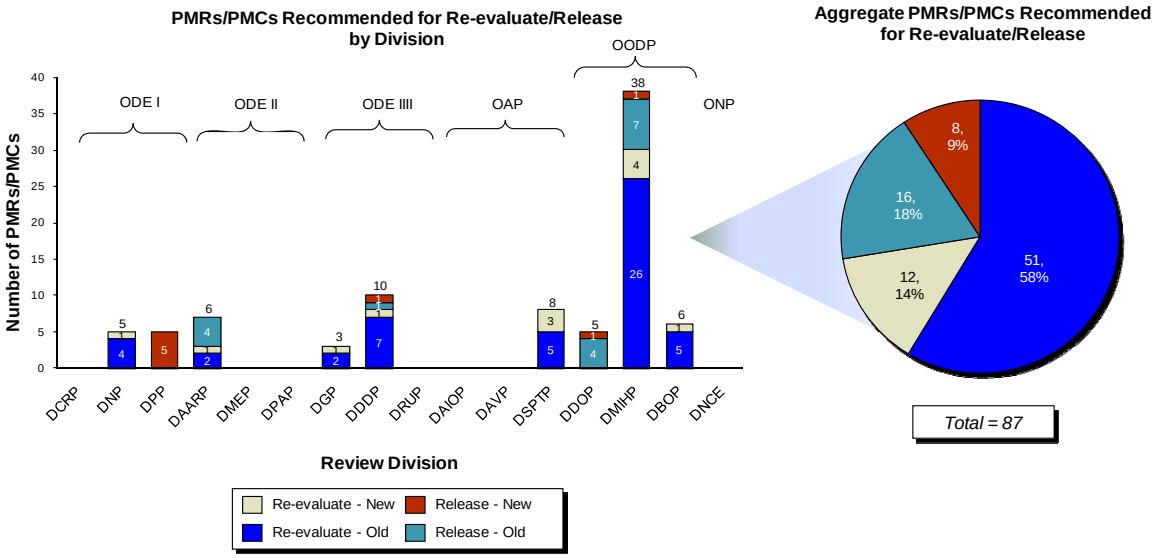
Exhibit 24: Re-evaluate and Release Recommendations by PMR/PMC Age



Most of the PMRs/PMCs recommended for re-evaluation and release were in the Divisions of Medical Imaging and Hematology Products (DMIHP) and Dermatology and Dental Products (DDDP) (Exhibit 25). Of those recommended for release, 33% (8/24) were in DMIHP, 88% of

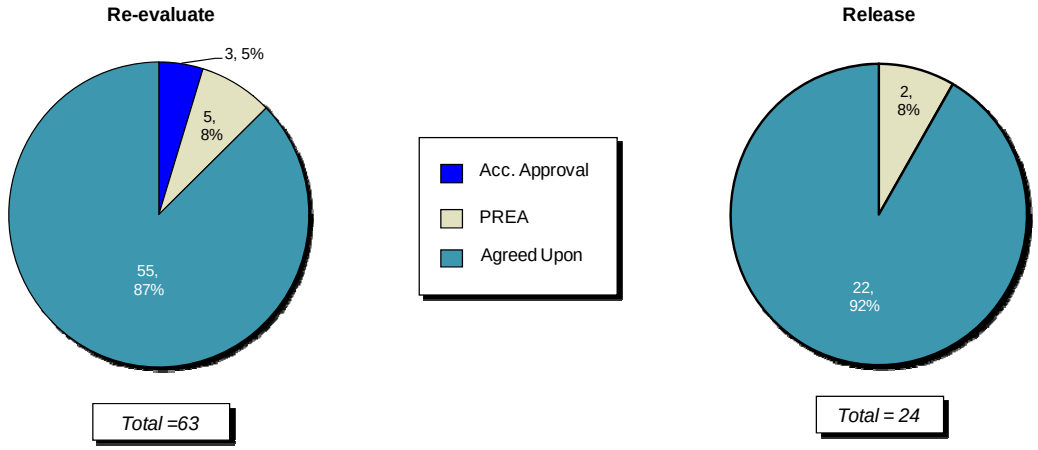
those were from the first annual Backlog review. Additionally, 48% (30/63) of PMRs/PMCs recommended for re-evaluation were in DMIHP. DSPTP and DDDP were each responsible for 13% (8/63) of those recommended for re-evaluation.

Exhibit 25: Re-evaluate and Release Recommendations by Review Division



Most of the studies/trials recommended for re-evaluation (87%) and release (92%) were agreed-upon PMCs (Exhibit 26).

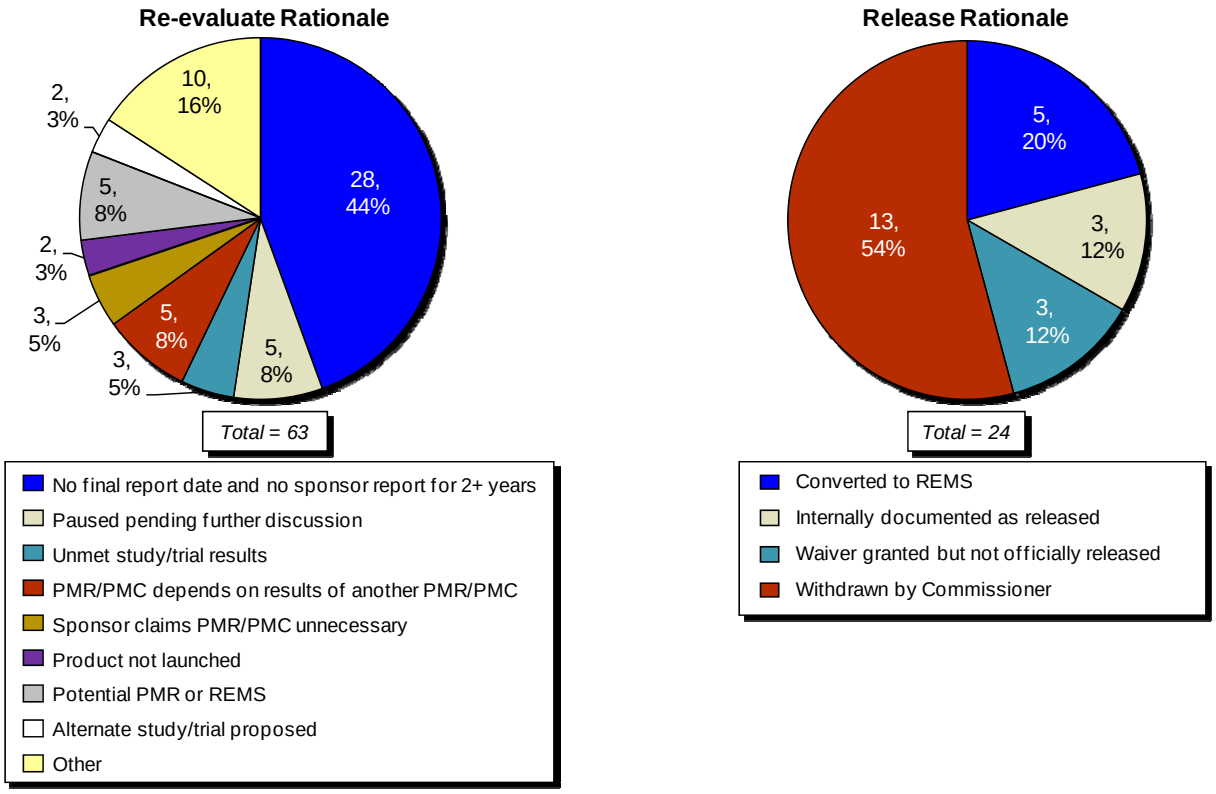
Exhibit 26: Re-evaluate and Release Recommendations



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

Many (44%) of PMRs/PMCs recommended for re-evaluation did not have final report submission dates and the largest segment (54%) of the release recommendations were issued because the product was withdrawn from the market (Exhibit 27).

Exhibit 27: Reason for Recommendation



5. KEY FINDINGS AND IMPLICATIONS/RECOMMENDATIONS

This second annual review of the PMR/PMC backlog yielded a number of key findings among those discussed in the previous sections. In particular, the comparison of the data from the first and second reviews demonstrated a consistency in certain areas (e.g., proportion of delayed PMRs/PMCs, divisions with highest numbers of submitted final reports), but also provided an opportunity to examine changes over the elapsed time between the reviews in other areas (e.g., progression in status throughout the PMR/PMC lifecycle). These key findings and their implications are highlighted in the table in Exhibit 28, along with recommendations to address them, where appropriate.

Exhibit 28: Key Findings and Implications/Recommendations

	Key Findings From Backlog Reviews	Implications/Recommendations
Off-schedule PMRs/PMCs	• After completion of the first and second annual Backlog reviews, approximately one-sixth of Backlog PMRs/PMCs are delayed. • Seventy-eight percent remained delayed from first review to second review • Only 7% of PMRs/PMCs that were on-schedule after first annual review became delayed during the course of second review • Certain divisions (e.g., DBOP, DAVP) consistently have a disproportionately high number of off-schedule PMRs/PMCs	• Some PMRs/PMCs will continue to be classified as delayed due to circumstances outside of sponsors' control (e.g., enrollment difficulties, supply issues) • FDA should record actual milestone dates in the PMR/PMC databases, such as when patient enrollment actually started or the final report was submitted, to capture the history of the conduct of the PMR/PMC and quickly respond to requests for this information • FDA could further investigate the PMRs/PMCs that linger in delayed status to determine if there are particular factors or characteristics of these PMRs/PMCs that could be avoided or mitigated for future PMRs/PMCs • The number of delayed PMRs/PMCs may be overstated because of inconsistent approaches to PMR/PMC closure • Investigate the PMR/PMC internal processes and procedures from these divisions to determine whether their practices are consistent with other review divisions
Submitted Final Reports	• More than 75% of the final reports in both reviews had been received more than 12 months ago • Certain divisions (e.g., DNP, DSPTP, DDDP) have a consistently high number of submitted final reports	• Sponsors must wait for FDA review of the final report before receiving feedback regarding important safety information that may impact the safe use of the product (e.g., labeling revisions) • FDA should consider prioritizing PMR/PMC review efforts on those final reports that have been submitted for more than 12 months, only after reviewing those final reports that have the highest impact on the safety profile of the product
Re-evaluate Recommend-ations	• The largest segment of re-evaluate recommendations in both reviews were issued because the PMR/PMC had no final report date and there was no sponsor report for more than 2 years	• FDA should issue Dunner letters to the sponsors for these PMRs/PMCs to evaluate progress towards completion • FDA should contact the sponsor via phone/email if the sponsor does not respond to the Dunner letter issued by FDA • By adhering to the PMR/PMC development and tracking MAPPs[18] (e.g., establishing milestone dates, conducting multiple levels of review) for future PMRs and PMCs, FDA could reduce the need to re-evaluate the requirements and commitments.

[18] MAPP 6010.2R. *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments.* July 28, 2009. and MAPP 6010.9. *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*. March 9, 2009.

	Key Findings From Backlog Reviews	Implications/Recommendations
Release Recommend-ations	• The largest segment of release recommendations in both reviews were issued because the product had been Withdrawn by the Commissioner	• FDA should prioritize review of those PMRs/PMCs that received release recommendations since these PMRs/PMCs may be closed out quickly

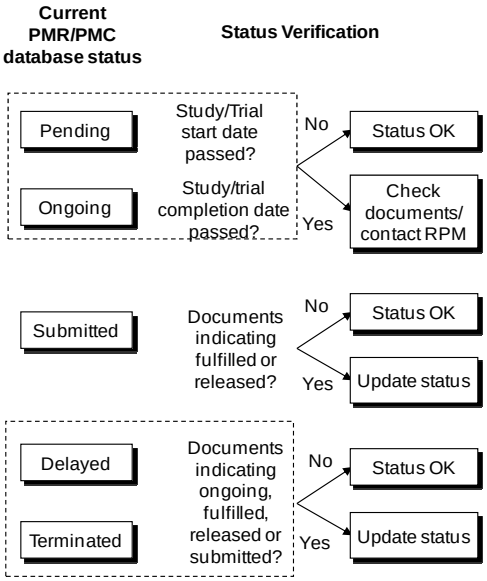
Appendix A: Detailed Procedures and Approach for the PMR/PMC Backlog Review

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 29). 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 29: 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., protocols, final 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 start or finish milestone passed. The gathered data

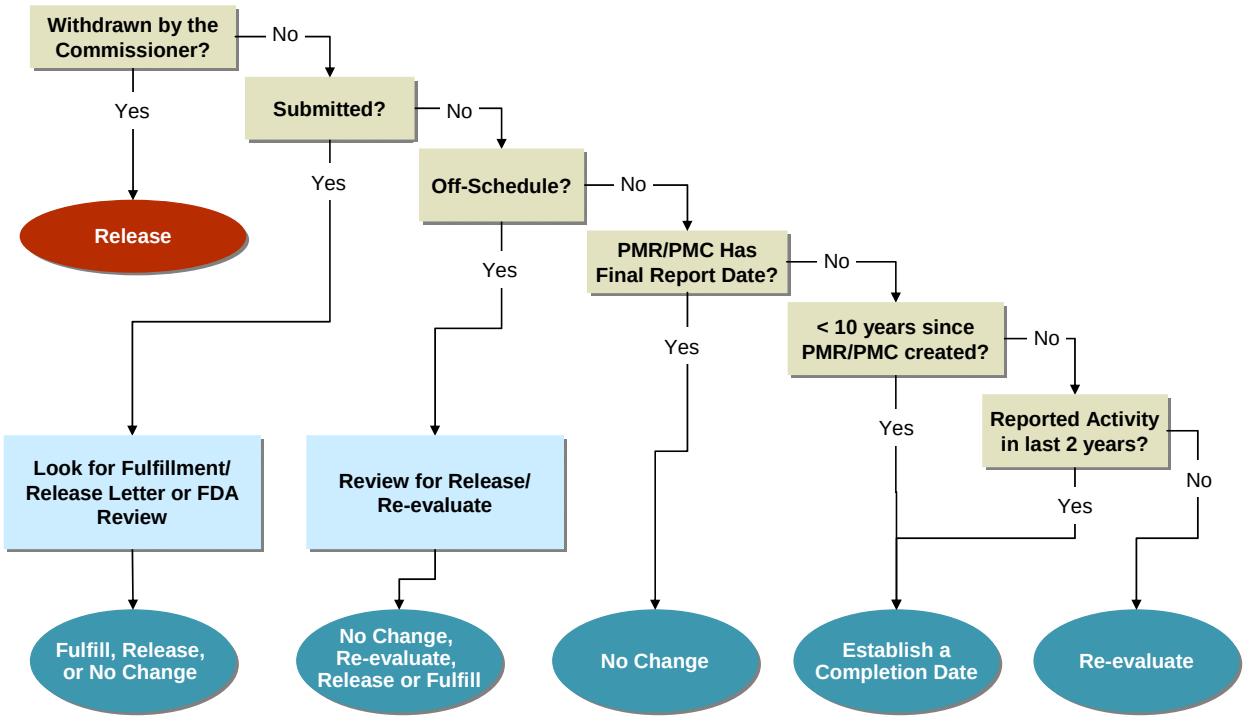
[19] Any PMR/PMC that was classified as pending in the PMR/PMC database, and had either no milestone dates or only a final report date was considered to have an uncertain status.

were stored in a data collection instrument (DCI), which was also used to 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 30). Based on this prioritization scheme, certain PMRs/PMCs were evaluated for potential re-evaluation or release.

Exhibit 30: 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 fulfillment 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 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 31, were documented, along with standard corresponding recommendations, to promote consistency in the review.

Exhibit 31: PMR/PMC Backlog Recommendation Scenarios

Scenario	Recom-mendation	Standard Approach	Rationale	Example PMRs/PMCs
Reviewer has internally documented a review of the PMR/PMC submission and that the PMR/PMC was fulfilled	Fulfill	Recommend review division issue a fulfill letter to sponsor and close the PMR/PMC	As the PMR/PMC has been reviewed and agreed to be fulfilled, notification should be sent to the sponsor and the PMR/PMC should be closed	• NDA 20554 (Dovonex) PMC# 1
A waiver (e.g., PREA) was granted but the PMR/PMC has not been officially released	Release	Recommend the review division issue a release letter.	Since the PMR/PMC has been waived, FDA should send the sponsor a release letter and close the PMR/PMC.	• NDA 21897 (Vivitrol) PMC #1
Converted to REMS	Release	Recommend the review division issue a letter outlining the REMS and release the PMR/PMC.	The PMR/PMC is identified as a potential REMS.	• NDA 21880 (Revlimid) PMC #5
Reviewer has internally documented agreement with a sponsor request for PMR/PMC release	Release	Recommend review division issue a release letter	As the PMR/PMC has been reviewed and agreed to be released, notification should be sent to the sponsor and the PMR/PMC should be closed	• NDA 22041 (Cyanokit) PMC# 3

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

Scenario	Recom-mendation	Standard Approach	Rationale	Example PMRs/PMCs
The product has been withdrawn by the commissioner	Release	Recommend the review division issue a release letter.	Since the PMR/PMC has been waived, FDA should send the sponsor a release letter and close the PMR/PMC.	• NDA 20887 (Acutect) PMCs #1, 2, 3, 4, 5, 6, 7
Contingency PMR/PMC	Re-evaluate	Review the original PMRs/PMCs and recommend the review division to re-evaluate the contingency PMR/PMC if the original PMR/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 PMR/PMC, the contingency PMR/PMC should be re-evaluated.	• NDA 21829 (Neupro) PMC #9
FDA has revised the PMR/PMC and/or proposed new timelines	Re-evaluate	Recommend the review division re-evaluate the PMR/PMC and determine if it should be released and re-written or retained.	PMR/PMC description and/or timelines have been revised extensively by FDA.	• NDA 21415 (Metvixia) PMC #2
No activity has occurred on an old (i.e., >10 years) PMC	Re-evaluate	Recommend the review division re-evaluate the need for PMR/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	• NDA 20084 (Iobenguane Sulfate) PMCs #3,4,5,6,7,8,9
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 PMR/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.	• NDA 20732 (Subutex) PMC #2
Sponsor has requested market withdrawal, but FDA has not responded	Re-evaluate	Sponsors often stop conducting the PMRs/PMCs if the product is withdrawn from the market. The review division should issue an acknowledgement letter to facilitate the withdrawal process. The PMR/PMC should be re-evaluated to determine if the PMR/PMC can be released after it has been	The sponsor requested withdrawal of the application, so the PMR/PMC may no longer be necessary.	• NDA 20686 (Lumenhance) PMC #1

Scenario	Recom-mendation	Standard Approach	Rationale	Example PMRs/PMCs
		formally withdrawn.		
Sponsor has requested release from PMR/PMC and there is no indication that the study/trial is proceeding	Re-evaluate	Classify PMR/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.	• NDA 21191 (Imagent Kit/Prep of Perflexane Lipid) PMC #5
Unmet results	Re-evaluate	The review division should re-evaluate the PMR/PMC to determine whether FDA should release the current PMR/PMC and issue a new PMR/PMC, or keep the PMR/PMC open and issue a new PMR/PMC.	Even though the results were insufficient to satisfy the PMR/PMC as fulfilled, the PMR/PMC should be re-evaluated to see if a revision is necessary.	• BLA 125084 (Erbitux) PMC #1
PMR/PMC lacks a final report date, but recent activity has occurred on an old (i.e., >10 years) PMR/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 PMR/PMC has been created for a while, the recent activities demonstrate the PMR/PMC is in progress	• NDA 50737 (Neoral) PMCs #2, 3
PMR/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	PMRs/PMCs without milestones are difficult to track, and cannot be satisfied and closed	• Ongoing Registry ✓ NDA 21302 (Elidel) PMC #1 • Study/trial with no established milestones ✓ NDA 20639 (Seroquel) PMC #4
Due to difficulty with patient enrollment, FDA plans to allow different studies/trials to be submitted in support of the PMR/PMC	No Change	Look for the correspondence that documents the agreed upon alternative studies/trials and FDA should note in eventual fulfill letter that the replacement studies/trials did meet the original objectives.	Studies/trials that support the intended PMR/PMC objective can be submitted to support fulfillment of the PMR/PMC.	• BLA 103767 (Ontak) PMC #2
Final report was submitted less than 12 months	No Change	• Confirm FDA receipt of final report and identify document location	The final report should be reviewed within 12 months of	• BLA 103000 (Botox) Seq. 5050 PMC #1

Scenario	Recom-mendation	Standard Approach	Rationale	Example PMRs/PMCs
ago, but not reviewed		(e.g., in EDR or Document Room). Request from offsite document room if necessary. • Remind division PMR/PMC Tracking Coordinator of outstanding submissions needing review	receipt.	
Final report was received more than 12 months ago	No Change	• Confirm FDA receipt of final report and identify document location (e.g., in EDR or Document Room). Request from offsite document room if necessary. • Remind division PMR/PMC Tracking Coordinator of outstanding submissions needing review	FDA guidance recommends final reports be reviewed within 12 months of receipt	• NDA 19949 (Diflucan) PMCs# 1,2,4,5,6,9
PMR/PMC is on-schedule and has a final report date	No Change	No immediate action	The PMC is progressing on schedule.	• NDA 20272 (Risperdal) Seq. 36 PMC #3
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	• NDA 21264 (Apokyn) PMC # 18
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.	• NDA 21882 (Exjade) PMCs #5, 7

Appendix B: Office of New Drugs Review Division Key

Exhibit 32: Division Abbreviation Key

Division Abbreviation	Full Division Name
DCRP	Division of Cardiovascular and Renal Products
DNP	Division of Neurology Products
DPP	Division of Psychiatry Products
DAARP	Division of Anesthesia, Analgesia, and Rheumatology Products
DMEP	Division of Metabolic and Endocrinology 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 Urologic 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 of Nonprescription Clinical Evaluation