

Report to Senate Committee on Health, Education, Labor, and Pensions and
the House Committee on Energy and Commerce

Report on the Fourth Review of the Backlog of Postmarketing Requirements and Commitments
by the
Food and Drug Administration
2012

Submit to HHS for review and concurrence before final signature:

_____ **Date** _____
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Commissioner of Food and Drugs

Introduction

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). Section 921 of Title IX of FDAAA amends section 505(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(k)) by adding a provision requiring the Food and Drug Administration (FDA) to “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.” FDA has reviewed the backlog that consists of all postmarketing requirements (PMRs) and postmarketing commitments (PMCs) that were open (not yet released or fulfilled) as of the date of enactment of FDAAA. PMRs and PMCs are studies or clinical trials required of (PMRs) or agreed upon (PMCs) by an applicant that are conducted after FDA has approved a product for marketing. These studies and clinical trials are intended to further define the safety, efficacy, or optimal use of a product and, therefore, play an important role in fully characterizing the product. FDA has identified 1,637 PMRs/PMCs (1,554 in the Center for Drug Evaluation and Research (CDER) and 83 in the Center for Biologics Evaluation and Research (CBER)) that comprise the backlog to which section 921 applies.¹ This is the fourth annual report on the review of the backlog of postmarketing requirements and commitments. Past reports are available at the following web pages:

First Annual Report:

[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketing PhaseIVCommitments/UCM2915522.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM2915522.pdf)

Second Annual Report:

[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketing PhaseIVCommitments/UCM291520.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM291520.pdf)

Third Annual Report :

[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketing PhaseIVCommitments/UCM324917.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM324917.pdf)

The data available for review of the backlog of PMRs and PMCs are constantly changing as submissions are reviewed and statuses are updated. This report is based on a cohort of data that had a data lock date of September 30, 2011. The fourth annual report shows that as of September 30, 2011, the required review for CDER had been completed for all 1,554² PMRs and

¹ Before FDAAA, all postmarketing studies and clinical trials (both required and agreed upon) were referred to as postmarketing commitments. Therefore, the backlog of postmarketing commitments includes required studies and clinical trials as well as those studies/clinical trials an applicant agreed to, but was not required to, conduct. Since FDAAA, the terminology has been clarified to distinguish those studies/clinical trials that are required from those that are agreed upon. Before FDAAA, PMRs/PMCs specifically addressing safety issues were not separately identified; therefore, the backlog includes both PMRs/PMCs intended to address safety issues as well as those addressing nonsafety issues (e.g., efficacy studies).

² In the second annual backlog review, which was completed on March 12, 2010, the external contractor who conducted the review determined that the CDER backlog cohort consisted of 1,551 PMRs and PMCs. During the third annual review, CDER discovered one PMR/PMC that did not qualify as a PMR/PMC and was subsequently

PMCs in the backlog. CBER reviewed its backlog of 83 PMRs and PMCs, and the results of that review are also included in this report.

Background

Section 130(a) of the Food and Drug Administration Modernization Act of 1997 amended the FD&C Act by adding a new provision requiring reports of certain postmarketing studies for human drug and biological products (section 506B of the FD&C Act (21 U.S.C. 356(b))). Section 506B of the FD&C Act provides FDA with authority to monitor the progress of a PMC by requiring the applicant to submit an annual report providing information on the status of the PMC, which was defined to include agreed-upon commitments and required studies (including clinical trials).³

This annual report that applicants submit must also include the reasons, if any, for failure to satisfy the commitment. This provision is implemented at 21 CFR 314.81(b)(2)(vii) and 601.70.⁴ Under section 506B(b) and (c), FDA is required to track these PMCs and report on them annually in the *Federal Register*.⁵ As described previously, as of the date of enactment of FDAAA, there were 1,637 (CDER and CBER) open PMRs and PMCs that are considered the backlog for purposes of the section 921 backlog review.⁶

The backlog includes both PMRs and PMCs. PMRs and PMCs are studies or clinical trials required of (PMRs) or agreed upon (PMCs) by an applicant that are conducted after FDA has approved a product for marketing. These studies and clinical trials are intended to further define the safety, efficacy, or optimal use of a product and, therefore, play an important role in fully characterizing the product.

Before the passage of FDAAA, FDA required studies or clinical trials in the following situations:

removed from this cohort. During the fourth annual review, CDER discovered four additional PMR/PMCs that had previously been excluded from the backlog (e.g., never entered into the database).

³ See the guidance for industry *Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*, available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077374.pdf.

⁴ In addition, new drug application applicants are required by 21 CFR 314.81(b)(2)(viii) to report annually to FDA on postmarketing studies or clinical trials that are not 506B studies or clinical trials. Such studies or clinical trials are not required, and they include chemistry, manufacturing, and controls (CMC) studies that applicants have agreed with FDA to conduct (CMC commitments), and all product stability studies that applicants have agreed with FDA to conduct (stability studies). The reporting requirement under 21 CFR 314.81(b)(2)(viii) also includes “any postmarketing study not included under [§314.81(b)(2)(vii) . . . that is being performed by, or on behalf of, the applicant.” Reports on the status of these types of studies are not reports required under section 506B.

⁵ The reports are available on the Internet at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm064436.htm

⁶ At the outset of this evaluation, CDER provided a list of 1,643 open PMRs and PMCs derived from the internal PMR/PMC tracking systems as of September 27, 2007. During the course of the annual reviews, CDER identified a number of PMRs/PMCs that were erroneously included in (e.g., duplicate entry, previously released/fulfilled study/clinical trial, non-PMR/PMC element from action letter) or excluded from this group (e.g., never entered into database). After these corrections were made, the CDER backlog consisted of 1,554 PMRs/PMCs.

- Subpart H and subpart E accelerated approvals for products approved under section 505(b) of the FD&C Act or section 351 of the Public Health Service Act, respectively, which require postmarketing studies to demonstrate clinical benefit (21 CFR 314.510 and 601.41, respectively);
- Deferred pediatric studies, where studies are required under the Pediatric Research Equity Act (PREA); and
- Animal efficacy rule approvals, where studies to demonstrate safety and efficacy in humans are required at the time of use (21 CFR 314.610(b)(1) and 601.91(b)(1)).

Under FDAAA, FDA has been given additional authority to require applicants to conduct and report on postmarketing 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 product. These required safety studies/clinical trials, as well as those required under accelerated approval, the animal rule, and PREA, as described above, are now considered PMRs. Studies or clinical trials required after the passage of FDAAA are not included in the annual backlog review because the *backlog* has been interpreted in this context to refer to all required or agreed-upon studies or clinical trials that had not been released or fulfilled before the passage of FDAAA.

Methodology

The first and second annual CDER reviews were conducted by an external contractor who reviewed internal FDA systems and documents to determine the current status for all PMRs/PMCs. This was accomplished by first identifying the status of each 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 existing documentation, e.g., PMR/PMC annual status reports, PMR/PMC final study/clinical trial reports, FDA-applicant communications, and internal FDA memos and reviews.

After the accurate statuses were determined, additional review of the backlog of PMRs/PMCs was performed to identify candidates for revision or release.⁷ Those PMRs/PMCs that were off-schedule, (i.e., delayed or terminated) or had no milestone dates, were prioritized for review over those that were on-schedule, (i.e., pending, ongoing, or submitted) based on established milestone dates. The contractor provided CDER with the results of the review as well as recommendations regarding potential re-evaluation or release of PMRs/PMCs in the backlog. CDER conducted the third and fourth annual reviews and continued to monitor the progress of the PMRs/PMCs recommended for revision or release in addition to assessing the current status for the entire backlog.

CBER has a comprehensive module in its biologics license application database system for tracking PMRs/PMCs. Information from the system is extracted monthly and quarterly, and is subjected to quality control processes external to the review offices for Center and FDA reports.

⁷ There were 1049 PMRs/PMCs that did not require a review because they were determined to be already fulfilled or released.

This, along with clearly defined CBER staff responsibilities for managing PMRs/PMCs, helps to ensure that data available from the system are relatively current and accurate.

Findings

CDER

- As of September 30, 2011, the number of open PMRs/PMCs in the backlog continues to decrease. As seen in Table 1 and Figure 1, the aggregate status of the backlog of PMRs/PMCs was as follows: five percent (77/1,554) of the backlog PMRs/PMCs were categorized as pending, seven percent (106/1,554) ongoing, 13 percent (199/1,554) delayed, less than one percent (10/1,554) terminated, seven percent (113/1,554) submitted, 53 percent (827/1,554) fulfilled, and 14 percent (222/1,554) released. By comparison, the data as of September 30, 2010 (the data lock date for the third annual review), showed six percent (93/1,550) of the backlog PMRs/PMCs were categorized as pending, nine percent (132/1,550) ongoing, 14 percent (223/1,550) delayed, less than one percent (13/1,550) terminated, 13 percent (197/1,550) submitted, 45 percent (701/1,550) fulfilled, and 12 percent (191/1,550) released. (See Appendix A for the status definitions.)
- Of the 183 pending or ongoing PMRs/PMCs in the CDER backlog, there were 58 (32 percent) that had no specific milestones or completion date by which to determine PMR/PMC status.
 - These 58 PMRs/PMCs remain in a pending or ongoing status category because there was no final report or other milestone by which to make a status determination of delayed.
 - Although 52 percent (802/1,554) of the PMRs/PMCs in the CDER backlog were created between fiscal years 2004 and 2007, only 3 (5 percent) of the 58 pending or ongoing PMRs/PMCs without completion dates were created during this time period, reflecting improved documentation of milestone dates in recent approval letters.
- Only 10 percent (49/505) of the open CDER backlog PMRs/PMCs were recommended for re-evaluation by CDER reviewers because of possible issues with feasibility or relevance, suggesting that the vast majority of PMRs/PMCs were sufficiently well-conceived when established.

Table 1: CDER PMR/PMC Statuses After Annual Reviews

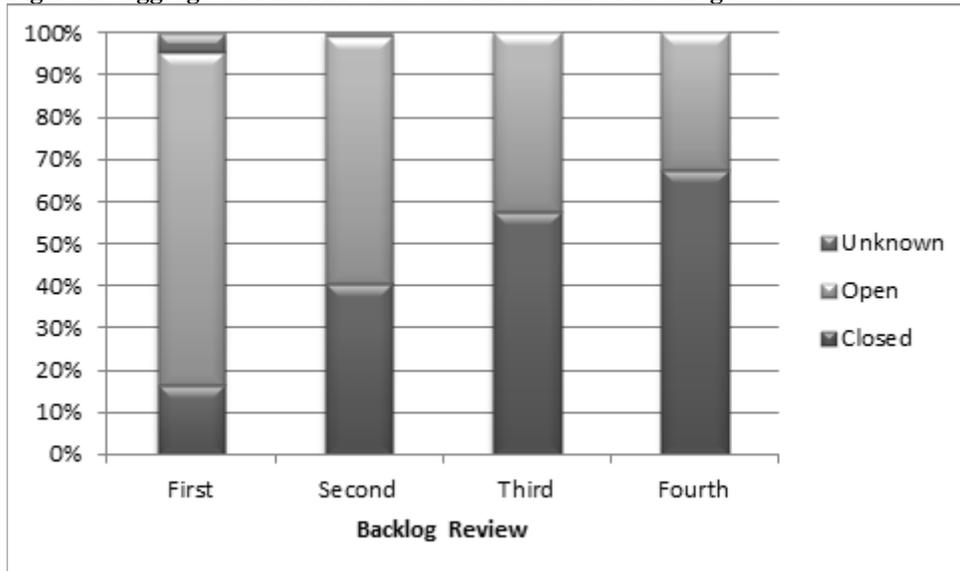
PMR/PMC Status	Number of PMRs/PMCs After First Review	Number of PMRs/PMCs After Second Review	Number of PMRs/PMCs After Third Review	Number of PMRs/PMCs After Fourth Review ¹
Pending	208	114	93	77
Ongoing	212	156	132	106
Submitted	565	366	197	113
Delayed	225	264	223	199
Terminated	16	13	13	10
Fulfilled	209	483	701	827
Released	47	146	191	222
Undetermined ²	39	9	0	0
Not Available ³	30	0	0	0
Total	1,551	1,551	1,550	1554

¹ During the course of the fourth annual review, CDER discovered four PMR/PMCs that had previously been excluded from the backlog (e.g., never entered into the database). After this correction was made, the CDER backlog consisted of 1,554 PMRs/PMCs.

² After the first and second annual reviews, the status of 39 and 9 PMRs/PMCs, respectively, was undetermined because of insufficient documentation to determine the correct status at the time of the backlog review. During the third annual review, CDER determined the status of these remaining nine undetermined PMRs/PMCs.

³ The status of 30 PMRs/PMCs was not available after the first annual review because the PMRs/PMCs had not been entered into the PMR/PMC database. These PMRs/PMCs were subsequently entered and reviewed.

Figure 1: Aggregate PMR/PMC Statuses After Annual Backlog Reviews



Unknown = PMR/PMC Status Unknown or Undetermined

Open = PMR/PMC Status of Pending, Ongoing, Delayed, Submitted or Terminated

Closed = PMR/PMC Status of Released or Fulfilled

- During the course of the fourth annual review, the status of 211 PMRs/PMCs changed as a result of study/trial initiation or completion, final report submission, or missed milestone date. For those PMR/PMC statuses that were updated, 60 percent (126/211) were updated to fulfilled, 15 percent (31/211) were updated to released, nine percent (18/211) were updated to delayed, five percent (10/211) were updated to ongoing, one percent (2/211) were updated to pending, 11 percent were updated to submitted (23/211), and less than one percent (1/211) were updated to terminated. The 126 PMR/PMC statuses updated to fulfilled reflect a significant effort from the review divisions to complete reviews of the large number of submitted final reports identified during the third annual review.
- Only four percent (18/422) of PMRs/PMCs that were on-schedule after the third annual review became delayed during the course of the fourth review.
 - Two of the 18 PMRs/PMCs that became delayed were previously pending.
 - Both missed final report submission milestone date.
 - Nine of the 18 PMRs/PMCs that became delayed were previously ongoing.
 - Seven missed the final report submission milestone date and two are progressing on a revised schedule.
 - Seven of the 18 PMRs/PMCs that became delayed were previously submitted.
 - All became delayed after the review division determined the final report did not satisfy the requirements of the PMR/PMC and the final report submission milestone date had passed.
- The updated status data show that 68 percent (1049/1,554) of PMRs/PMCs have been closed (i.e., fulfilled or released) and 83 percent (418/505) of the open PMRs/PMCs have either studies/trials initiated or completed (i.e., ongoing, delayed or had final reports submitted) at the time of the fourth annual review.

CBER

As of September 30, 2011, the fourth annual review showed the status for the backlog of CBER's 83 PMRs/PMCs was 2 percent pending, 8.5 percent ongoing, 8.5 percent submitted, 22 percent delayed, 2 percent released and 57 percent fulfilled (100 percent). The comparison between the status data shown in Table 2 suggests that most PMRs/PMCs statuses have been updated by the review offices based on information obtained through the applicants' annual status reports or review of the final study report submissions. Table 2 also indicates 59 percent of the PMRs/PMCs in the backlog have been closed (Fulfilled + Released).

Of the 83 PMRs/PMCs, 27 (33 percent) were without an original projected completion date. A recommendation was previously presented to the CBER offices to obtain a complete schedule for the missing dates. This effort reduced the number to three (four percent) without a projected completion date. Since the enactment of FDAAA, CBER's PMRs/PMCs without a schedule are dependent on some initializing condition such as a protocol agreement date. In addition, CBER is continuing its efforts to oversee the management of PMRs/PMCs within the center through its quality control processes along with management oversight through the CBER FDAAA Safety Work Group.

Table 2: CBER PMR/PMC Statuses After Annual Reviews

PMR/PMC Status	Number of PMRs/PMCs After First Review	Number of PMRs/PMCs After Second Review	Number of PMRs/PMCs After Third Review	Number of PMRs/PMCs After Fourth Review
Pending	10	5	4	2
Ongoing	21	19	18	7
Submitted	24	14	14	7
Delayed	23	23	18	18
Terminated	0	0	0	0
Fulfilled	5	22	29	47
Released	0	0	0	2
Total	83	83	83	83

Conclusions

- As of September 30, 2011, 68 percent (1049/1554) of the PMRs/PMCs in the CDER backlog have been closed (i.e. fulfilled or released).
- Most (418/505, 83 percent) open CDER PMRs/PMCs in the backlog have a study/clinical trial in progress, delayed, or completed, or await CDER review of the applicant-submitted final report.
- For those PMR/PMC statuses in the CDER backlog that were updated, more than half (60 percent) 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 prior annual reviews.
- Only 10 percent (49/505) of the open CDER backlog PMRs/PMCs were recommended for re-evaluation by CDER reviewers because of possible issues with feasibility or relevance, suggesting that the vast majority of PMRs/PMCs were sufficiently well-conceived when established.
- All Office of New Drug review divisions have developed a plan for completion of review of the CDER backlog and for the management of PMR/PMC issues in general. For the 197 PMR/PMC final reports received as of September 30, 2010, 54 percent (107/197) had either been reviewed or were under review and 50 percent (98/197) were closed (either fulfilled or released) as of September 30, 2011.

After completion of the fourth annual review, the number of open CDER and CBER PMRs/PMCs in the backlog decreased from 44 percent (712/1,633)⁸ to 33 percent (539/1,637). The number of open PMRs and PMCs will continue to diminish each year as applicants complete studies/trials and submit final reports and FDA reviews the final reports and issues fulfillment and release letters.

⁸ The total number of CDER and CBER PMRs/PMCs (1,633) does not include the four CDER PMRs/PMCs discovered during the course of the fourth annual backlog review.

Appendix A: PMR/PMC Status Definitions*

PMR/PMC Status	Definition
Pending	The study/clinical trial has not been initiated, but does not meet the criterion for delayed.
Ongoing	The study/clinical trial is proceeding according to or ahead of the original schedule.
Submitted	The study/clinical trial has been completed or terminated and a final study report has been submitted to FDA.
Delayed	The study/clinical trial is behind the original schedule.
Terminated	The study/clinical trial was ended before completion but a final study report has not been submitted to FDA.
Fulfilled	The final report for the study/clinical trial was submitted to FDA and FDA notified the applicant that the commitment was fulfilled through written correspondence.
Released	FDA has informed the applicant in writing that it is released from its obligation to conduct the study/clinical trial because the study/clinical trial is no longer feasible, would no longer provide useful information, or the underlying application has been withdrawn.

*Adapted from 21 CFR 314.81.