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

Report on the Third Review of the Backlog of Postmarketing Requirements and Commitments

by the

Food and Drug Administration

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Introduction

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA) of 2007 (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 1,633 PMRs/PMCs (1,550 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 third 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/PostmarketingPhaseIVCommitments/UCM291522.pdf

Second Annual Report:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PostmarketingPhaseIVCommitments/UCM291520.pdf

The data available for review of the backlog of PMRs and PMCs is 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, 2010. The third annual report shows that as of September 30, 2010, the required review for CDER had been completed for all 1,550[2] PMRs and 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.

[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 removed from this cohort.

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 1,633 (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:

- 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,

[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/default.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 first, second, and third 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 1,550 PMRs/PMCs.

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) (21 CFR 314.55(b) and 601.27(b)); 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 annual review 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. 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.

[7] There were 892 PMRs/PMCs that did not require a review because they were determined to be already fulfilled or released.

Findings

CDER

- As of September 30, 2010, the aggregate status of the backlog of PMRs/PMCs was as follows: 6 percent (93/1,550) of the backlog PMRs/PMCs were categorized as pending, 9 percent (132/1,550) ongoing, 14 percent (223/1,550) delayed, less than 1 percent (13/1,550) terminated, 13 percent (197/1,550) submitted, 45 percent (701/1,550) fulfilled, and 12 percent (191/1,550) released. By comparison, the data as of December 21, 2009 (the data lock date for the second annual review), showed 7 percent (114/1,551) of the backlog PMRs/PMCs were categorized as pending, 10 percent (156/1,551) ongoing, 17 percent (264/1,551) delayed, less than 1 percent (13/1,551) terminated, 24 percent (366/1,551) submitted, 31 percent (483/1,551) fulfilled, and 9 percent (146/1,551) released.[8] (See Table 1 for annual review comparisons; see Appendix A for the status definitions.)

- Of the 225 pending or ongoing PMRs/PMCs in the CDER backlog, there were 67 (30 percent) that had no specific milestones or completion date by which to determine PMR/PMC status.

    - These 67 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 (800/1,550) of the PMRs/PMCs in the CDER backlog were created between fiscal years 2004 and 2007, only 4 (6 percent) of the 67 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 9 percent (56/658) 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.

[8] The second annual backlog review final report was completed on March 12, 2010.

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[1]
Pending	208	114	93
Ongoing	212	156	132
Submitted	565	366	197
Delayed	225	264	223
Terminated	16	13	13
Fulfilled	209	483	701
Released	47	146	191
Undetermined[2]	39	9	0
Not Available[3]	30	0	0
Total	1,551	1,551	1,550

[1] During the course of the third annual review, CDER determined that one PMR/PMC did not qualify as a PMR/PMC and was subsequently removed. After this correction was made, the CDER backlog consisted of 1,550 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 9 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 during the second and third annual reviews.

- During the course of the third annual review, the status of 376 PMRs/PMCs changed as a result of study/trial initiation or completion, final report submission, or missed milestone dates. For those PMR/PMC statuses that were updated, 58 percent (218/376) were updated to fulfilled, 12 percent (45/376) were updated to released, 9 percent (32/376) were updated to delayed, 6 percent (21/376) were updated to ongoing, 2 percent (8/376) were updated to pending, 13 percent were updated to submitted (50/376), and 1 percent (2/376) were updated to terminated. The 218 PMR/PMC statuses updated to fulfilled PMRs/PMCs reflect a significant effort from the review divisions to complete reviews of the large number of submitted final reports identified during the second annual review.

- Only 5 percent (29/636) of PMRs/PMCs that were on-schedule after the second annual review became delayed during the course of the third review.

    - Eleven of the 29 PMRs/PMCs that became delayed were previously pending
        - Reasons include missed protocol submission milestone date, missed trial/study start milestone date, and missed final report submission milestone date.
    - Twelve of the 29 PMRs/PMC that became delayed were previously ongoing
        - Four missed the final report submission milestone date and eight are progressing on a revised schedule.
    - Six of the 29 PMRs/PMC 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 58 percent (892/1,550) of PMRs/PMCs have been closed (i.e., fulfilled or released) and 84 percent (552/658) 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 third annual review.

CBER

As of September 30, 2010, the third annual review showed the status for the backlog of CBER's 83 PMRs/PMCs was 4 percent pending, 22 percent ongoing, 17 percent submitted, 22 percent delayed, and 35 percent fulfilled (100 percent). By comparison, the data as of December 31, 2009 (the data lock date for the second annual review), showed the status for the backlog during the second review was 6 percent pending, 23 percent ongoing, 17 percent submitted, 28 percent delayed, and 26 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 35 percent of the PMRs/PMCs backlog has been closed.

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 continuous effort reduced the number to 3 (4 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
Pending	10	5	4
Ongoing	21	19	18
Submitted	24	14	14
Delayed	23	23	18
Terminated	0	0	0
Fulfilled	5	22	29
Released	0	0	0
Total	83	83	83

Conclusions

- Most (552/658, 84 percent) open CDER PMRs/PMCs in the backlog have a study/clinical trial in progress, delayed, completed, or are awaiting CDER review of the applicant-submitted final report.
- For those PMR/PMC statuses in the CDER backlog that were updated, more than half (58 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 the first and second annual reviews.
- Only 9 percent (56/658) 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 366 PMR/PMC final reports received as of December 21, 2009, 60 percent (219/366) had been reviewed and 58 percent (213/366) were closed (either fulfilled or released) as of September 30, 2010.
- As of September 30, 2010, 58 percent of the CDER backlog has been closed (i.e. fulfilled or released).

After completion of the third annual review, the number of open CDER and CBER PMRs/PMCs in the backlog decreased from 60 percent (974/1,634)[9] to 44 percent (712/1,633). 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.

[9] The total number of CDER and CBER PMRs/PMCs (1,634) includes the one CDER PMR/PMC that CDER determined did not qualify as a PMR or PMC during the third 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.