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

Report on the Second 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 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. FDA has identified 1,634 PMRs/PMCs (1,551 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 second annual report on the review of the backlog of postmarketing requirements and commitments.

This report is based on a report prepared for FDA by Booz Allen Hamilton (BAH), a contractor hired to perform the backlog review for CDER. BAH's first and second reports on the CDER backlog review are available on the FDA Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PostmarketingPhaseIVCommitments/ucm064436.htm. 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 December 21, 2009. The second annual report shows that as of December 21, 2009, the required review for CDER had been completed for all 1,551[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.

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

[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 first annual backlog review, which was completed on April 10, 2009, BAH determined that the CDER backlog cohort consisted of 1,531 open PMRs and PMCs. During the second annual review, BAH discovered additional PMRs/PMCs that were erroneously included in or excluded from this group.

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 1,634 (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, 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

[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 http://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 http://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 and second annual review, the contractor 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 1,551 PMRs/PMCs.

- 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

CDER employed the same external contractor that performed the first annual review to perform the second annual review of its 1,551 PMR/PMC backlog. During the CDER backlog review, the contractor 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.

CBER has a relatively small PMR/PMC backlog. As a result, CBER chose to perform its own internal review rather than participate in the CDER contract.

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.

Findings

CDER

- As of February 22, 2009, 13 percent (208/1,551) of the backlog PMRs/PMCs were categorized as pending, 14 percent (212/1,551) ongoing, 15 percent (225/1,551) delayed,

[7] There were 629 PMRs/PMCs that did not require a review because they were determined to be already fulfilled or released.

less than 1 percent (16/1,551) terminated, 36 percent (565/1,551) submitted, 13 percent (209/1,551) fulfilled, and 3 percent (47/1,551) released.[8] (See Appendix A for the status definitions.)

- After reviewing and updating PMR/PMC status for accuracy (as of the December 21, 2009, data lock date), the aggregate status of the backlog of PMRs/PMCs was 7 percent (114/1,551) 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. (See Table 1 for a first and second annual review comparison.)

Table 1: CDER PMR/PMC Statuses After First and Second Annual Review

PMR/PMC Status	Number of PMRs/PMCs After First Review[1]	Number of PMRs/PMCs After Second Review
Pending	208	114
Ongoing	212	156
Submitted	565	366
Delayed	225	264
Terminated	16	13
Fulfilled	209	483
Released	47	146
Undetermined[2]	39	9
Not Available[3]	30	0
Total	1,551	1,551

[1] The number of PMRs/PMCs after the first review for each status category were previously reported as follows: 211 pending, 213 ongoing, 569 submitted, 226 delayed, 16 terminated, 210 fulfilled, 47 released, 39 undetermined, and 0 not available. During the second review, the contractor determined that there were PMRs/PMCs inaccurately included in the first annual review and these were removed for the following reasons:

- The PMR/PMC was a duplicate 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

[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.

[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 annual review.

- During the course of the second annual review, the status of 591 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, nearly half (46 percent, 273/591) 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 annual review.

[8] The first annual backlog review final report was completed on April 10, 2009.

- Only 7 percent (67/985) of PMRs/PMCs that were on-schedule after the first annual review became delayed during the course of the second review.

    - Thirty-three of the 67 PMRs/PMCs that became delayed were previously pending
        - Eight missed the protocol submission milestone date
        - Seven missed the trial/study start milestone date
        - Eighteen missed the final report submission milestone date
    - Twenty of the delayed PMRs/PMCs were previously ongoing
        - All 20 missed the final report submission milestone date
    - Fourteen of the delayed PMRs/PMCs were previously submitted
        - All 14 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

- After the second review, 86 percent (227/264) of the delayed PMRs/PMCs are off-schedule because of a missed final report milestone date, whereas only 1 percent (3/264) are delayed because of a missed study/clinical trial completion date. Out of the PMRs/PMCs that are delayed because of a missed final report milestone date, 53 percent (120/227) had studies/trials in progress.

- The updated status data show that 40 percent (629/1,551) of PMRs/PMCs have been closed, i.e., fulfilled or released and 72 percent (656/913) of the open PMRs/PMCs have either studies/trials initiated or completed, i.e., ongoing, delayed with study/trial in progress or completed or had final reports submitted at the time of the second annual review.

- Of the 1,551 PMRs/PMCs in the CDER backlog, there were 466 (30 percent) that had no specific milestones or completion date by which to determine PMR/PMC status. This led to a significant number of requirements/commitments remaining indefinitely 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 half of the PMRs/PMCs in the CDER backlog were created between 2004 and 2007, only 37 (8 percent) of the 466 PMRs/PMCs without completion dates were created during this time period.

- The contractor provided one out of five possible recommendations (i.e., release, fulfill, re-evaluate, establish milestone dates, or no change) for each of the remaining open PMRs/PMCs (913/1,551) that required a review.

    - The majority (81 percent, 740/913) of PMRs/PMCs in the backlog were recommended for no change because they were proceeding according to their original schedule, submitted awaiting CDER review of the final report, or off-schedule but still progressing toward completion.

- Only 63 (7 percent) were recommended for re-evaluation, which required CDER reviewers to assess the necessity and feasibility of the current study/clinical trial and specify the appropriate course of action (e.g., replace the PMR/PMC with a new, more feasible one).

- For the entire PMR/PMC backlog, only 4 percent (35/913) of the open PMRs/PMCs received a recommendation of fulfill or release. A recommendation of fulfill or release was made only when a fulfillment or release determination was identified in internal documentation, e.g., a review memo and no official fulfillment or release letter had been sent to the applicant.

- Of the 122 PMRs/PMCs that lacked a final report submission milestone date, 61 percent (75/122) were issued a recommendation to proceed with the study/clinical trial but establish a completion date, because the investigations were being actively conducted. For the remaining PMRs/PMCs in the subset, the contractor recommended that the review divisions re-evaluate the necessity and feasibility of the studies/clinical trials for 25 percent (30/122), release the PMR/PMC for 10 percent (12/122) and fulfill the PMR/PMC for 4 percent (5/122).

- Eighty-one percent (51/63) of the recommendations for re-evaluation issued in the second annual report were repeat recommendations from the first annual report on which FDA had not yet taken action. This is likely because of the emphasis placed on review of the submitted final reports and issuance of fulfillment, nonfulfillment, and release letters after the first backlog review.

- During the course of the second annual review, the contractor also contacted each review division to follow-up on each recommendation issued in the first annual review to determine what action, if any, was taken by the division based on the recommendation. In the first annual backlog review, the contractor issued re-evaluate recommendations for 74 PMRs/PMCs. Among these PMRs/PMCs, 24 percent (18/74) were either released or scheduled for release, and 20 percent (15/74) have either held discussions or scheduled discussions to determine whether the PMR/PMC should remain open or be closed. Of the 20 PMRs/PMCs that received a fulfill recommendation in the first annual review, 7 (35 percent) were issued fulfillment letters notifying the applicant of closure of the PMR/PMC. For those PMRs/PMCs where the recommendation was considered but rejected, the review division noted that the applicant still had more to do before the PMR/PMC could be fulfilled. The action taken on 39 percent (11/28) of the PMRs/PMCs that received a release recommendation was issuance of a release letter.

CBER

As of June 11, 2009, the status for the backlog of CBER's 83 PMR/PMCs during the first review was 12 percent pending, 25 percent ongoing, 29 percent submitted, 28 percent delayed, and 6 percent fulfilled (100 percent). Based on the data lock date of December 31, 2009, the second review shows the status for the backlog PMRs/PMCs 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 25 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 presented to the CBER offices to obtain a complete schedule for the missing dates. This effort reduced the number to 8 (10 percent) without a projected completion date. CBER is actively working on the remainder of the missing milestone due dates. 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 Before and After Review

PMR/PMC Status	Number of PMRs/PMCs After First Review	Number of PMRs/PMCs After Second Review
Pending	10	5
Ongoing	21	19
Submitted	24	14
Delayed	23	23
Terminated	0	0
Fulfilled	5	22
Released	0	0
Total	83	83

Conclusions

- Most (656/913, 72 percent) open CDER PMRs/PMCs in the backlog have a study/clinical trial in progress, have a study/trial completed, or await CDER review of the applicant-submitted final report.

- For those PMR/PMC statuses that were updated, nearly half (46 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 annual review.

- Only 7 percent 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 backlog and for the management of PMR/PMC issues in general. Internal goal dates were established to complete the review of all PMR/PMC final reports received as

of June 30, 2009 (total of 621 PMRs/PMCs).[9] As of November 2010, 82 percent (507/621) had been reviewed and 76 percent (470/621) were closed (either fulfilled or released).

- As of December 21, 2009, 40 percent of the CDER backlog has been closed.

After completion of the second annual review, the number of open CDER and CBER PMRs/PMCs in the backlog decreased from 81 percent (1,304/1,604)[10] to 60 percent (974/1,634). 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] This number includes final reports received after the December 21, 2009, data lock date for the second backlog review.

[10] The total number of CDER and CBER PMRs/PMCs (1,604) does not include the 30 CDER PMRs/PMCs that were not in the PMR/PMC database at the time the first annual review was completed (see Table 1). These PMRs/PMCs were subsequently entered and reviewed during the second annual 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.