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

Report on the Review of the Backlog of Postmarketing Requirements and Commitments by FDA

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 (the Act) (21 U.S.C. 355) 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 which 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. FDA has identified 1,614 [1531 in the Center for Drug Evaluation and Research (CDER), 83 in the Center for Biologics Evaluation and Research (CBER)] PMRs/PMCs that comprise the backlog to which section 921 applies.[1] This is the first annual report on the review of the backlog of postmarketing requirements and commitments.

This report is based on a report prepared for the agency by Booz Allen Hamilton (BAH), a contractor hired to perform the backlog review for CDER. BAH's first report on the CDER backlog review is available on the FDA Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm180982.htm#. The data available for review of the backlog of PMRs and PMCs is constantly changing as submissions are reviewed and statuses are updated. The report is based on a cohort of data with a data lock date of February 22, 2009. The report shows that as of that date, the required review for CDER had been completed for 1,492 (97 percent) of the 1,531 PMRs and PMCs in the backlog. Review of the remaining 39 commitments continued after the data lock date, and the results will be included in the second annual review of the backlog, which is nearing completion. CBER reviewed its backlog of 83 PMRs and PMCs, and the results of that review are also reported herein.

Background

Section 130(a) of the Food and Drug Administration Modernization Act of 1997 amended the Act by adding a new provision requiring reports of certain postmarketing studies for human drug and biological products (section 506B of the Act (21 U.S.C. 356(b)). Section 506B of the 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).[2]

[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 a safety issue as well as those addressing nonsafety issues (e.g., efficacy studies).

[2] See *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* (guidance on the status of PMCs), available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.

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.[3] Under section 506B(b) and (c), FDA is required to track these PMCs and report on them annually in the Federal Register.[4] As described previously, as of the date of enactment of FDAAA, there were 1,614 (CDER and CBER) open PMRs and PMCs that are considered the backlog for purposes of the section 921 backlog review.[5]

The backlog includes both PMRs and PMCs. PMRs and PMCs are studies or clinical trials required of an applicant (PMRs) or agreed to by an applicant (PMCs) 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 505(b) of the 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);

- 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 to studies or clinical trials that had not been released or fulfilled before the passage of FDAAA.

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[3] 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.

[4] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

[5] 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 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 1,531 PMRs/PMCs.

Methodology

CDER employed an external contractor to perform the first annual review of its 1531 PMR/PMC backlog. During the CDER backlog review, the contractor initially 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 conducted to identify items for revision or release.[6] 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 reevaluation or release of PMRs/PMCs in the backlog.

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

CBER has a comprehensive module in its Biologic License Applications (BLA) 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 Agency reports. This, along with clearly defined CBER staff responsibilities for managing PMRs/PMCs, helps to assure that data available from the system are relatively current and accurate.

Findings

CDER

- As of September 27, 2007, 64 percent of the backlog PMRs/PMCs were categorized as pending, 15 percent ongoing, 14 percent submitted, 7 percent delayed, and less than 1 percent terminated. (See Appendix A for the status definitions.)

- After reviewing and updating PMR/PMC status for accuracy, the aggregate status of the backlog PMRs/PMCs was 14 percent pending, 14 percent ongoing, 36 percent submitted, 15 percent delayed, 14 percent fulfilled, 3 percent released and 1 percent terminated. (See Table 1 for a before-and-after review comparison.)

[6] There were 257 PMRs/PMCs that did not require a review because they were determined to be already fulfilled or released.

Table 1: CDER PMR/PMC Statuses Before and After Review

PMR/PMC Status	Number of PMRs/PMCs Before Review	Number of PMRs/PMCs After Review
Pending	967	211
Ongoing	231	213
Submitted	220	569
Delayed	103	226
Terminated	4	16
Fulfilled	0	210
Released	0	47
Undetermined[1]	6	39

[1] The status of six PMCs was undetermined before the review because the PMCs had not been entered into the PMR/PMC database. These were subsequently entered and reviewed. After the review, the status of 39 PMRs/PMCs was undetermined because of insufficient documentation to determine the correct status at the time of the backlog review.

- The updated status data show that at the time of the review (June 2008 through February 22, 2009), most PMRs/PMCs that remained open as of September 27, 2007, had been initiated and more than half of them had been submitted, fulfilled, or released.

- Of the CDER PMR/PMC backlog, there were 458 (30 percent) that had no specific milestones or completion dates, which led to a significant number of requirements/commitments remaining indefinitely in a pending or ongoing status category.

- Although half of the PMRs/PMCs in the CDER backlog were created during the previous 4 years, only 36 (8 percent) of the 458 PMRs/PMCs without completion dates were created during this time period.

- The contractor provided one out of five possible recommendations (release, fulfill, re-evaluate, establish milestone dates, or no change) for each of the remaining 1,235 PMRs/PMCs that required a review. The vast majority (81 percent, 998/1,235) 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 74 (6 percent) were recommended for reevaluation, 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 (48/1,235) of the 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 159 on schedule PMRs/PMCs that lacked a final report submission date, 72 percent (115/159) were issued a recommendation to proceed with the study/clinical trial because the investigations were being actively conducted, but the sponsors were asked to provide the agency with a completion date. The contractor recommended that the review divisions reevaluate the necessity and feasibility of the remaining 28 percent (44/159) of the studies/clinical trials that had not reported activity over the prior 2 years.

CBER

On the date FDAAA was enacted, 14 percent of CBER's backlog of 83 PMRs/PMCs were categorized as pending, 42 percent ongoing, 17 percent submitted, and 27 percent delayed. As of June 11, 2009, the PMR/PMC status for the backlog PMRs/PMCs was 12 percent pending, 25 percent ongoing, 29 percent submitted, 28 percent delayed, and 6 percent fulfilled (100 percent). The comparison between the status data shown in table 2 suggests that most PMRs/PMCs have been updated by the review offices from ongoing to submitted, and 6 percent of the backlog updated to fulfilled based on normal submission activity.

Of the 83 PMRs/PMCs, 27 (33 percent) are without an original projected completion date. A recommendation will be presented to the CBER offices to obtain a complete schedule for the missing dates. Since the enactment of FDAAA, CBER has had 13 approvals with 26 PMRs/PMCs. Only 5 (19 percent) of the 26 PMRs/PMCs are without an original schedule. The schedules, including the projected completion date for these 5, are dependent on some initializing condition such as a protocol agreement date. In addition, CBER has established a Safety Work Group (SWG) to oversee the management of PMRs and PMCs within the Center.

Table 2: **CBER PMR/PMC Statuses Before and After Review**

PMR/PMC Status	Number of PMRs/PMCs Before Review	Number of PMRs/PMCs After Review
Pending	12	10
Ongoing	35	21
Submitted	14	24
Delayed	22	23
Terminated	0	0
Fulfilled	0	5
Released	0	0

Conclusions

- Most CDER PMRs/PMCs in the backlog are either progressing toward completion of the study/clinical trial or were already completed and await CDER review of the applicant-submitted final report.

- Only 6 percent of the 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.

- Although a substantial number of PMRs/PMCs in the CDER backlog require the creation of completion dates, the number of new PMRs/PMCs established without completion dates has declined dramatically over the last several years as the CDER PMR/PMC development policies and processes have been more widely implemented. For CBER, study schedules are often written with reference to the protocol agreement date. Since the enactment of FDAAA, CBER has taken steps to closely monitor the protocol agreement date in order to establish and document subsequent schedule dates.

- Additional process improvements have already been implemented in CDER and CBER, including the following:

  - PMR/PMC development coordinators and PMR/PMC tracking coordinators have been assigned to each CDER Office of New Drugs (OND) review division.

  - Harmonized internal procedures have been developed and are being implemented to more efficiently develop, track, and review PMR/PMC annual status reports and final reports across Centers. CDER published MAPP 6010.9 *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments* (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm). CBER developed SOPP 8415: *Procedures for Developing Postmarketing Requirements and Commitments.* (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073519.htm)

  - In addition to staff training, groups are meeting regularly to review shared issues and to share best practices. The intent is to improve consistency in developing PMRs/PMCs that will, in turn, lead to better informed studies/clinical trials with effective designs and realistic time frames.

  - The contractor worked with the divisions to facilitate review of all CDER PMRs/PMCs with submitted status.

- All CDER OND review divisions have developed a plan for completion of review of the backlog and for the management of PMR/PMC issues in general. An internal goal date of June 30, 2010, has been established to complete the review of all PMR/PMC final reports submitted on or before June 30, 2009.

- As of October 8, 2009, more than one-third of the CDER backlog (36 percent) has been closed.

Together, these observations and improvements suggest that with each subsequent annual review, the backlog of 1,614 PMRs/PMCs (defined as those PMRs/PMCs that were not yet released or fulfilled as of the date of enactment of FDAAA) will diminish, until such time as all 1,614 have either been fulfilled or released.

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	The study/clinical trial was formally released by FDA

*Adapted from 21 CFR 314.81.