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

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

by the

Food and Drug Administration

(Data through: September 30, 2015)

_____ Date _____

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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 "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." FDAAA requires FDA to complete these tasks on an annual basis.

The "backlog" 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.[1] 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 identified 1,637 PMRs/PMCs that comprise the backlog to which section 921 applies (1,554[2] in the Center for Drug Evaluation and Research (CDER) and 83 in the Center for Biologics Evaluation and Research (CBER)). This is the eighth annual report on the review of the backlog of postmarketing requirements and commitments. The report includes information about PMRs/PMCs in the backlog that remain open, as well as those that were closed (see Appendix A for these definitions). Past reports are available here:

First Annual Report
Second Annual Report
Third Annual Report
Fourth Annual Report
Fifth Annual Report
Sixth Annual Report
Seventh Annual 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. During the fourth annual review, CDER discovered four additional PMR/PMCs that had previously been excluded from the backlog (e.g., never entered into database). One additional PMR/PMC was discovered during the fifth annual review. This PMR/PMC was subsequently determined to be a duplicate and was removed from the cohort during the seventh annual review.

This report is for both the open and closed PMRs/PMCs in the backlog, and is based on data that had a data lock date of September 30, 2015.

Background

Section 130(a) of the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) 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. 356b)). 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]

These annual reports that applicants submit must also include the reasons for any failures 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]

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, so-called accelerated approval. These require postmarketing studies to verify clinical benefit (21 CFR 314.510 and 601.41, 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 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 FDA website at http://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 consists of 1,554 PMRs/PMCs, which together with the 83 CBER PMRs/PMCs forms the 1637 PMRs/PMCs that are the subject of this report.

- 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, PREA, and the animal rule, 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.

Methods

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 has conducted all subsequent annual reviews, including this eighth review, and continues to monitor the progress of the PMRs/PMCs recommended for revision or release in addition to assessing the current status for the entire backlog.

The data available for PMRs and PMCs in the backlog are constantly changing as submissions are reviewed and the statuses of the PMRs/PMCs are updated. CDER has policies and procedures to help ensure that its data on PMRs/PMCs, including data on the PMRs and PMCs in the backlog, are current and accurate. When identified, data discrepancies are addressed and/or are corrected in later reports. The information in this report reflects the status information in CDER's database at the time the data were extracted and can be considered to be reflective of CDER's data quality control processes.

[7] There were 1,049 PMRs/PMCs that did not require a review because they were determined to be already fulfilled or released.

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 Summary of Progress

- The number of open PMRs/PMCs in the CDER backlog continues to decrease. The data show that as of September 30, 2015, 90 percent (1,395/1,554) of PMRs/PMCs have been closed (i.e., fulfilled or released). Of the 159 PMRs/PMCs in the backlog that remain open, 74 percent (117/159) have either studies/trials in progress or completed (i.e., ongoing, delayed or had final reports submitted) at the time of the eighth annual review.

- As shown in Table 1 and Figure 1, as of September 30, 2015, the status of the CDER backlog of PMRs/PMCs was as follows: pending: 2 percent (32/1,554); ongoing: 2 percent (37/1,554); delayed: 4 percent (65/1,554); terminated: less than 1 percent (10/1,554); submitted: 1 percent (15/1,554); fulfilled: 68 percent (1050/1,554); and released: 22 percent (345/1,554). In comparison to the previous year,[8] 12 fewer PMRs/PMCs are ongoing and 32 more are fulfilled.

  The data for the previous year showed that 3 percent (49/1,554) of the CDER backlog PMRs/PMCs were categorized as pending, 3 percent (49/1,554) ongoing, 3 percent (49/1,554) delayed, less than 1 percent (8/1,554) terminated, 2 percent (30/1,554) submitted, 65 percent (1018/1,554) fulfilled, and 21 percent (327/1,554) released (see Appendix A for the status definitions).

[8] *See the Seventh Annual Backlog Report to Congress: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM472973.pdf.*

Table 1: CDER PMR/PMC Statuses After Annual Reviews

	Number of PMRs/PMCs After							
PMR/PMC Status	**First Review**	**Second Review**	**Third Review**	**Fourth Review[1]**	**Fifth Review[2]**	**Sixth Review**	**Seventh Review[3]**	**Eighth Review**
Pending[4]	208	114	93	77	51	46	49	32
Ongoing	212	156	132	106	71	60	49	37
Submitted	565	366	197	113	79	63	30	15
Delayed	225	264	223	199	171	124	73	65
Terminated	16	13	13	10	11	7	8	10
Fulfilled	209	483	701	827	900	953	1018	1050
Released	47	146	191	222	272	302	327	345
Undetermined[5]	39	9	0	0	0	0	0	0
Not Available[6]	30	0	0	0	0	0	0	0
Total	1,551	1,551	1,550	1,554	1,555	1,555	1,554	1,554

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

[2] During the course of the fifth annual review, CDER discovered one PMR/PMCs that had previously been excluded from the backlog (e.g., never entered into database). After this correction was made, the CDER backlog consists of 1,555 PMRs/PMCs.

[3] During the course of the seventh annual review, CDER discovered a duplicate PMR entry. After the duplicate entry was removed the CDER backlog totaled 1,554 PMRs/PMCs.

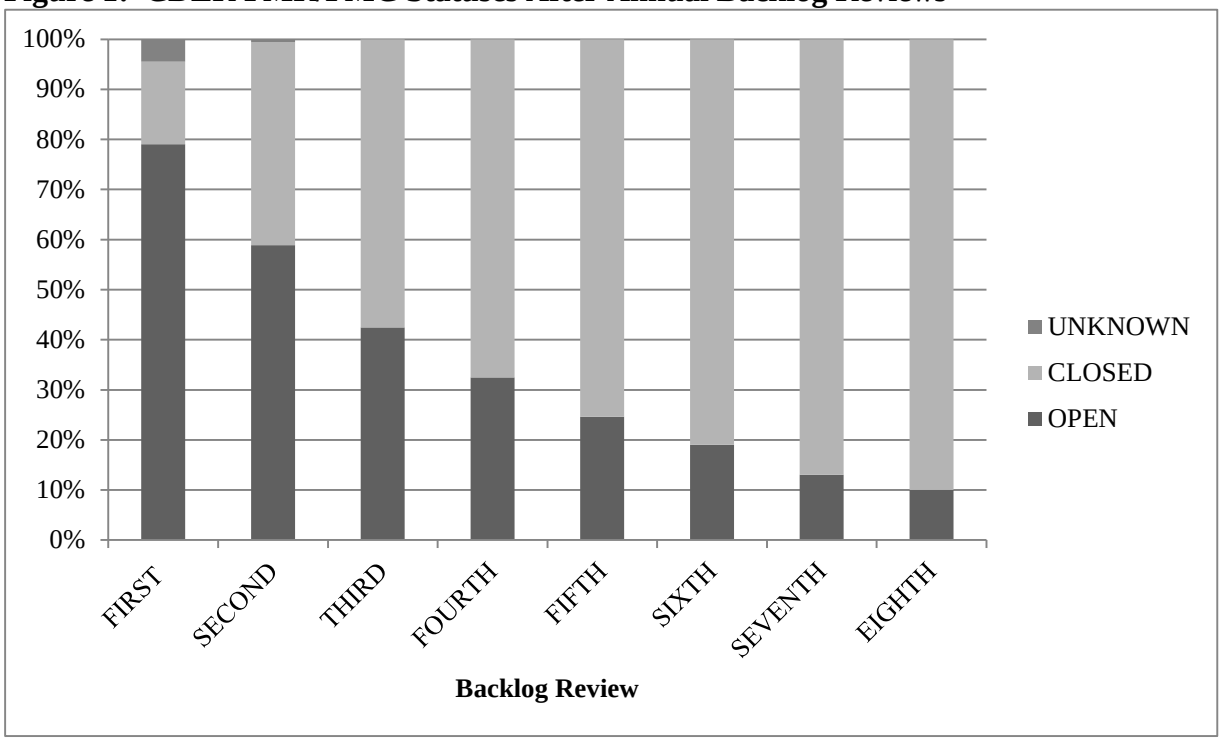
[4] PMRs in pending status include those issued under Pediatric Research Equity Act (PREA) and the animal efficacy rule (21 CFR 314.600 through 314.650 and 21 CFR 601.90 through 601.95). PREA PMRs are often deferred because the drug product is ready for approval in adults before pediatric studies are complete. Initiation of the PREA studies may also be deferred because FDA finds that pediatric studies should be delayed until additional safety or effectiveness data has been collected. Postmarket studies required under the animal efficacy rule are to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and the drug is used). In the absence of an emergency, these studies/clinical trials will remain pending indefinitely.

[5] 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.

[6] 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 displays the data from Table 1 in graphical form. Again, the figure shows that the number of open (i.e., pending, ongoing, delayed, terminated or submitted) PMRs/PMCs in the CDER backlog has progressively decreased. At the end of FY 2015, the number of open PMRs/PMCs in the CDER backlog decreased to 10% (159/1554) from 13% (209/1554) in the previous year.

Figure 1: CDER 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 eighth annual review, the status of 74 PMRs/PMCs in the CDER backlog changed (was updated) as a result of study/trial initiation or completion, final report submission, or missed milestone date.
    - For those PMR/PMC statuses that were updated, 49 percent (36/74) were updated to fulfilled, 28 percent (21/74) were updated to released, 8 percent (6/74) were updated to delayed, 1 percent (1/74) were updated to ongoing, 3 percent (2/74) were updated to pending, 7 percent were updated to submitted (5/74), and 4 percent (3/74) were updated to terminated.
    - Only 3 percent (4/128) of PMRs/PMCs that were on-schedule after the seventh annual review became delayed during the course of the eighth review.
    - The 36 PMR/PMC statuses updated to fulfilled reflect the consistent effort from the review divisions to complete reviews of the submitted final reports identified during the seventh annual review.

- Of the 79 pending, ongoing, or terminated PMRs/PMCs in the CDER backlog, there were 15 (19 percent) that had no specific milestones or completion date by which to determine PMR/PMC status.
    - These 15 PMRs/PMCs remain in a pending, ongoing, or terminated status category because there was no final report submission date or other milestone by which to make a status determination of delayed.

- These 15 PMRs/PMCs also represent 3 percent of the original 457[9] PMRs/PMCs in the CDER backlog that had no milestones or completion dates.[10]
- There was an 18 percent decrease (3/17) in open PMRs/PMCs without milestone completion dates between FY 2014 and FY 2015.[11]
    - This decrease between FY 2015 and FY 2014 was due to:
        - Fulfilment of 1 PMRs/PMCs
        - Release of 2 PMRs/PMCs

- During the first review of the backlog, 74 PMRs/PMCs were originally recommended for re-evaluation by CDER reviewers because of possible issues with feasibility or relevance,[12] suggesting that the vast majority of PMRs/PMCs were sufficiently well-conceived when established. Of these 74 PMRs/PMCs, 27 percent (20/74) remain open.
    - This represents a 23 percent (6/26) decrease since FY 2014 in the number of open PMRs/PMCs recommended for reevaluation.[13]
    - This decrease was the result of either fulfillment or release of the PMRs/PMCs during FY 2015. Of the 6 PMRs/PMCs originally recommended for re-evaluation and that were closed during this period, 17 percent (1/6) were released and 83 percent (5/6) were fulfilled.

In conclusion:

- Most (117/159, 74 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, 49 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.

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[9] The seventh annual review indicates that there were 458 PMRs/PMCs included in the original backlog cohort of PMRs/PMCs that had no milestones or completion dates. During the course of the eighth annual review, CDER discovered that one PMC should not have been included in this cohort because the PMC had a final protocol due date. Therefore, there were a total of 457 PMRs/PMCs in the original CDER backlog that had no milestones or completion dates.

[10] See *First Annual Backlog Report to Congress:* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM291522.pdf.

[11] Refer to the *Seventh Annual Backlog Report to Congress: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM472973.pdf.*

[12] See *First Annual Backlog Report to Congress:* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM291522.pdf.

[13] Refer to the *Seventh Annual Backlog Report to Congress: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM472973.pdf.*

- Only 13 percent (20/159) of the PMRs/PMCs that remain open in the CDER backlog were recommended for re-evaluation by CDER reviewers because of possible issues with feasibility or relevance, reflecting the consistent effort from the review divisions to complete reviews of final reports of final reports or other data that have subsequently been submitted and/or determine if these PMRs/PMCs can be released.

- 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 30 PMR/PMC final reports received as of September 30, 2014, 67 percent (20/30) had either been reviewed or were under review and 63 percent (19/30) were reviewed by FDA and the corresponding PMR/PMC determined to be closed (i.e., fulfilled or released) as of September 30, 2015.

CBER Summary of Progress

- The number of open CBER PMRs/PMCs in the backlog continues to decrease. The data show that as of September 30, 2015, 82 percent (68/83) of the PMRs/PMCs have been closed (i.e., fulfilled or released) and 93 percent (14/15) of the open PMRs/PMCs have studies/trials in progress or completed (i.e., ongoing, delayed or final reports submitted) at the time of the eighth annual review.

  The data in Table 2 and Figure 2 show the status for the backlog of CBER's 83 PMRs/PMCs was as follows: pending: 1 percent (1/83); ongoing: 4 percent (3/83); delayed: 8 percent (7/83); submitted: 5 percent (4/83); fulfilled: 80 percent (66/83); and 2 released: 2 percent (2/83). In comparison to the previous year,[14] 1 additional PMR/PMC was fulfilled.

- The data for the previous year showed 1 percent (1/83) of the backlog PMRs/PMCs were categorized as pending, 6 percent (5/83) ongoing, 9 percent (7/83) delayed, 4 percent (3/83) submitted, 78 percent (65/83) fulfilled, and 2 percent (2/83) released.

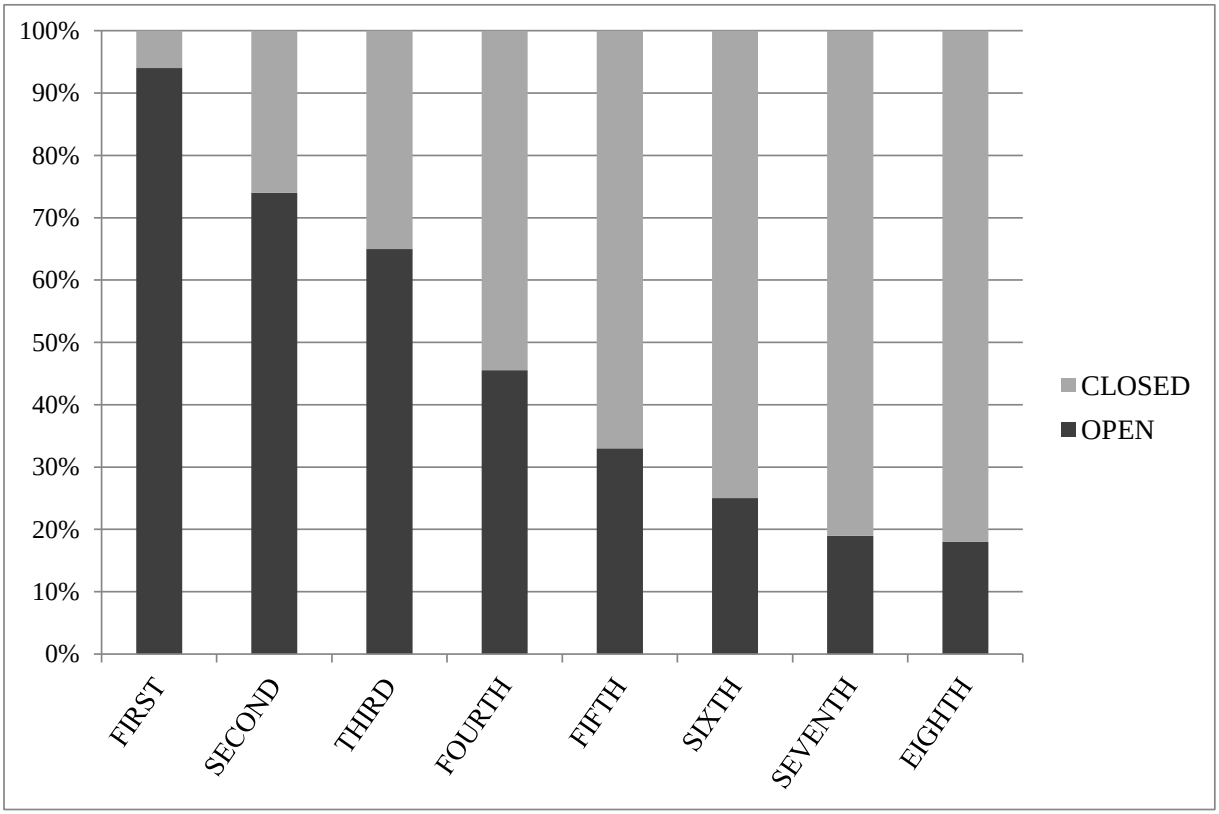
[14] *See the Seventh Annual Backlog Report to Congress* *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM472973.pdf*. .

Table 2: CBER PMR/PMC Statuses After Annual Reviews

	Number of PMRs/PMCs After							
PMR/PMC Status	First Review	Second Review	Third Review	Fourth Review	Fifth Review	Sixth Review	Seventh Review	Eighth Review
Pending	10	5	4	2	2	2	1	1
Ongoing	21	19	18	7	4	5	5	3
Submitted	24	14	14	7	8	3	3	4
Delayed	23	23	18	18	13	11	7	7
Terminated	0	0	0	0	0	0	0	0
Fulfilled	5	22	29	47	54	60	65	66
Released	0	0	0	2	2	2	2	2
Total	83	83	83	83	83	83	83	83

Figure 2 displays the data from Table 2 in graphical form. Again, the figure shows that the number of open PMRs/PMCs in the CBER backlog has progressively decreased. At the end of FY 2015, 18 percent (15/83) of the PMRs/PMCs in the backlog were open, which is down from 19 percent (16/83) at the end of FY 2014.

Figure 2: CBER PMR/PMC Statuses After Annual Backlog Reviews



- During the course of the eighth annual review, the status of 3 PMRs/PMCs changed as a result of study/trial initiation or completion or final report submission.
    - For those PMR/PMC statuses that were updated, one was updated to fulfilled, and two were updated to submitted.
- 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 3 (4 percent) without a projected completion date. The number of PMRs/PMCs without an original completion date did not change between FY 2015 and FY 2014.

In conclusion:

- All (15/15, 100 percent) open CBER PMRs/PMCs in the backlog have a study/clinical trial in progress, delayed, or completed, or awaiting CBER review of the applicant submitted final report.

Conclusions

- After completion of the eighth annual review, and as of September 30, 2015, 90 percent (1,395/1,554) of the PMRs/PMCs in the CDER backlog have been closed (i.e., fulfilled or released). Altogether, 82 percent (68/83) of the PMRs/PMCs in the CBER backlog have been closed.

- Since the previous fiscal year, the number of open PMRs/PMCs in the CDER backlog decreased to 10 percent (159/1554) from 13 percent (209/1554). The number of open PMRs/PMCs in the CBER backlog decreased to 18 percent (15/83) from 19 percent (16/83).

- 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.

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.
Open	PMR/PMC status of pending, ongoing, delayed, submitted or terminated.
Closed	PMR/PMC status of released or fulfilled.

*Adapted from 21 CFR 314.81.