What’s New in GCP?

FDA Reports Most Required Post-Approval Studies Are on Schedule

The majority of FDA-required post-approval studies — 86% of postmarketing requirements (PMR) studies and 77% of post-marketing commitment (PMC) studies — are on schedule, the agency reported Dec. 7.

“Most post-approval studies are on track,” Peter Stein, deputy director of the Center for Drug Evaluation and Research’s Office of New Drugs, said in an FDA Voice blog. “FDA will continue to work to ensure PMRs and PMCs are conducted as promptly as possible.”

Stein noted “many factors influence the timely conduct of a study, including low use of a product or changes in the standard of care, which can reduce the number of patients that can be studied. FDA assesses the justification for any delays and, if the justification is appropriate, monitors adherence to a revised timetable.”

According to FDA’s FY 2016 report on the performance of drug and biologics companies in conducting post-marketing studies, there were 285 unique applicants with open PMRs/PMCs under 890 unique New Drug Applications (NDAs) and Biologics License Applications (BLAs). There were 207 unique NDA applicants (and 734 associated applications) and 78 unique BLA applicants (and 156 associated applications) with open PMRs/PMCs.

Of the 622 NDA annual status reports (ASRs) due in that fiscal year, 66% (411/622) were received on time, 11% (66/622) were not received on time, and 23% (145/622) were not received during FY 2016. Of the 142 BLA ASRs due, 72% (102/142) were received on time, 17% (24/142) were not received on time, and 11% (16/142) were not received during FY 2016.

The FDA reported 84% of the open NDA PMRs and 91% of the open BLA PMRs were progressing on schedule, while 71% of the open NDA PMCs and 83% of the open BLA PMCs were on schedule.

Nearly half of the open NDA and BLA PMRs are pending, which means the study had not started but the original projected date of trial initiation had not passed. The FDA reported 49% of the open NDA PMRs and 45% of the open BLA PMRs are pending. Pediatric Research Equity Act (PREA) PMRs and FDA Amendments Act PMRs comprised 55% and 39% of pending PMRs, respectively. The next largest category of open and on-schedule PMRs were ongoing studies (29% of NDA PMRs and 37% of BLA PMRs).

In addition, 16% of the open NDA PMRs and 9% of the open BLA PMRs were off schedule. Of the off-schedule NDA PMRs, 97% were off schedule because they were delayed, and the rest were terminated. Similarly, 88% of the off-schedule BLA PMRs were delayed. “In certain situations, the original PMR schedules were adjusted for unanticipated delays in the progress of the study or clinical trial (e.g., difficulties with subject enrollment in a clinical trial for a marketed drug or the need for additional time to analyze results). In this report, study or clinical trial status reflects the status in relation to the original study or clinical trial schedule, regardless of whether FDA has acknowledged that additional time was required to complete the study or clinical trial,” the report noted.

The FDA also reported “most open, on-schedule NDA PMCs were pending (36%) and most open, on-schedule BLA PMCs were ongoing (43%). Fewer open NDA and BLA PMCs were considered off schedule (29% and 17%, respectively). The majority of off-schedule NDA and BLA PMCs were delayed, according to the original schedule milestones.
The majority of closed PMRs (72% of NDA PMRs and 82% of BLA PMRs) were fulfilled, meaning the final report for the study or clinical trial was submitted to the FDA, and the agency notified the applicant that the requirement or commitment was fulfilled. Similarly, most closed PMCs (82% of both NDA and BLA PMCs) were fulfilled at the end of FY 2016.

The FDA also reported that an average of 261 PMRs have been established each year since FY 2010, and most of the PMRs established in the earlier years were either fulfilled or released. For example, at the end of FY 2016, 54% of the PMRs that were established in FY 2010 were fulfilled, and 12% were released. “The majority of PMRs that were established in more recent years were either pending (i.e., not yet underway) or ongoing (i.e., still in progress and on schedule),” the FDA said. As of the end of FY 2016, 86% of the PMRs established in FY 2016 were pending, and 8% were ongoing. Overall, of the PMRs that were pending as of Sept. 30, 2016, 83% were created within the past three years. In addition, on average, 7% of the PMRs established since FY 2010 were delayed as of Sept. 30, 2016.

**Backlog Getting Better**

The FDA also released a report to Congress on the backlog of post-marketing requirements and commitments made prior to 2007 that indicated that, by Dec. 30, 2016, CDER completed the required review of 1,422 of 1,553 PMRs and PMCs in the backlog, and the Center for Biologics Evaluation and Research completed 71 of 83 PMRs and PMCs in the backlog. The CDER backlog decreased to 8% from 10% in the previous fiscal year.

"The number of open PMRs and PMCs will continue to diminish each year as applicants complete studies/trials and submit final reports and the FDA reviews the final reports and issues fulfillment and release letters,” the report said.

The FDA noted "the number of open PMRs/PMCs in the CDER backlog continues to decrease. As of Dec. 30, 2016, 92% of PMRs/PMCs have been closed (i.e., fulfilled or released). Of the 131 PMRs/PMCs that remain open, 76% have studies/trials either in progress or completed. However, 25 of the studies have not yet started and 54 are delayed. In the previous fiscal year, 32 studies had not been started and 65 were delayed.

During the year, the status of 48 PMRs/PMCs in the CDER backlog were updated as a result of study/trial initiation or completion, final report submission, or missed milestone date. Of these updated PMR/PMC statuses, 23% were updated to fulfilled, 39.5% were updated to released, 19% were updated to submitted, 12.5% were updated to delayed, and 6% were updated to ongoing. “The 11 PMR/PMC statuses updated to fulfilled reflect the consistent effort from the review divisions to complete reviews of the submitted final reports,” the FDA said.

Of the 58 PMR/PMCs with statuses of pending, ongoing or terminated, there were nine (16%) that had no specific milestones or completion date by which to determine the PMR/PMC status. The nine 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.” They represent 2% of the original 457 PMRs/PMCs in the CDER backlog that had no milestones or completion dates.

There also was a 44% decrease in open PMRs/PMCs without milestones or completion dates between FY 2015 and Dec. 30, 2016, due to fulfillment of one PMR/PMC and the release of six PMRs/PMCs.

The FDA noted that, "as a result of the first annual backlog review, 74 PMRs/PMCs were recommended for reevaluation 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. Of these 74 PMRs/PMCs, 24% remain open. This represents a
10% decrease since FY 2015 in the number of open PMRs/PMCs that were initially recommended for reevaluation.” Of the two PMRs/PMCs initially recommended for reevaluation and that were closed during this period, both were released.

**Other Recent Developments in the Guide to Good Clinical Practice**

FDA Issues Draft Guidance to Aid Trials for Targeted Medicines

Guidance Modifies FDA Criteria Used to Categorize IDE Devices for CMS Coverage Determinations

FDA Closes Orphan Drug Loophole