Food and Drug Administration

## Assessment of GRMPs Implementation

Evaluations and Studies of New Drug Review Programs Under PDUFA IV
for the Food and Drug Administration, Task Order 1, Order Number: HHSF223201010017B

# Final Report

**April 29, 2011**

Booz | Allen | Hamilton

# TABLE OF CONTENTS

# TABLE OF EXHIBITS

# 1. EXECUTIVE SUMMARY

Under the 2002 Prescription Drug User Fee Act (PDUFA III) Reauthorization Performance Goals and Procedures, FDA agreed to meet specific performance goals. Goal X, First Cycle Review Performance Proposal, of the PDUFA III goals, specified that FDA would create joint guidance for review staff and industry on good review management principles and practices (GRMPs) that apply to the first cycle review of New Drug Applications (NDAs), Biologics License Applications (BLAs) and efficacy supplements.[1] The GRMPs are intended to improve the effectiveness and efficiency of the first cycle review of new product applications by clarifying roles and responsibilities of review staff[2] in managing the review process. During the first review cycle, a well-managed review process allows sufficient time for careful regulatory decision-making, and if needed, time to work with the applicant to resolve readily correctable deficiencies in the application. The PDUFA III goals also specified that training must be provided to FDA staff in association with the implementation of GRMPs. In 2007, the CDER 21st Century Review process was rolled out to provide more information on how to execute a review consistent with the GRMPs activities and timeframes. CBER's review policies and procedures are executed through their Managed Review Process.

The NDA/BLA review process consists of five phases:

1) **Filing Determination and Review Planning Phase**: The activities in this phase are aimed at determining whether the application should be filed and planning the activities for the review along with their expected dates for completion.

2) **Review Phase:** In this phase the primary discipline reviewers conduct their review and share their findings with the review team. The primary review is completed when the secondary reviewer signs off on the review. There is typically an ongoing cycle of FDA information requests and sponsor-submitted amendments for review throughout this phase.

3) **Advisory Committee (AC) Meeting**: This phase includes the activities involved in planning, conducting, and disseminating information after an Advisory Committee meeting.

4) **Action Phase**: The action phase includes the final steps of the review cycle through the action taken on the application, including the wrap-up meeting, compilation of the action package, and signatory authority review of the action package and action letter.

5) **Post-Action Phase**: This phase includes optional activities that focus on lessons learned from the review process and discussions around subsequent submissions and review cycles for applications that were not approved.

The first four phases contain discrete activities that are to be completed by prescribed milestone dates to allow for sufficient time to perform the full application review. The post-action phase activities are not within the timeframe of PDUFA clock and do not have milestone dates associated with them.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf
[2] Review staff refers to all FDA personnel involved in reviewing an NDA or BLA, including regulatory project managers, discipline reviewers, consult reviewers and Office and Division Directors and Deputies.

## Study Overview

The key objective of this task was to assess the progress of CDER and CBER in fully implementing the GRMPs,[3] as well as certain PDUFA IV enhancements, focusing on both FDA review staff practices and industry sponsor practices affecting successful implementation.

To achieve this objective, this assessment consisted of the following activities:

- Determine the degree of current implementation of GRMPs by review divisions in CDER and CBER, including the parts of the GRMPs that divisions were already using before the promulgation and implementation of the GRMPs.
- Conduct a root-cause analysis to identify the main obstacles and enablers impacting GRMPs implementation.
- Recommend actions that would improve the effectiveness of the GRMPs implementation.

The degree of GRMPs implementation was determined by collecting and analyzing data from FDA documents and a regulatory project manager (RPM) questionnaire indicating the completion date of 42 selected GRMPs activities for a cohort of 61 original NDAs, BLAs and efficacy supplements. The 42 GRMPs activities that were used to assess implementation were based on the GRMPs Guidance for Review Staff and Industry, and are listed in Exhibit 2.[4] The applications chosen represent all review divisions and offices in both CDER and CBER, and were received in FY09 (October 1, 2008 – September 30, 2009) and reached first cycle action within a 12 month period (August, 2009 – July, 2010). These data were analyzed to assess compliance with the GRMPs, which was defined for the purpose of this analysis as completing the activity by the milestone date specified in the GRMPs guidance. Booz Allen conducted interviews with RPMs and focus groups with discipline reviewers to identify root causes for non-adherence of individual GRMPs activities. Booz Allen also interviewed applicant representatives of cohort applications and distributed a survey to FDA review staff.

It is important to note that this study did not, and was not intended to, evaluate the quality of the review, the scientific and medical evaluation, or the technical merit of the review decision. The array of activities and associated milestones in the GRMPs constitutes an important element of improving the effectiveness and efficiency of the NDA/BLA review process. However, these milestones are intended as guidelines in the process to facilitate the management of a timely

[3] The 21st Century Review is an initiative developed by CDER to provide standard activities required for NDA/BLA reviews, procedures to meet GRMPs, descriptions of roles and responsibilities of review staff and signatory authorities, and process improvements to promote a successful review process. As part of the 21st Century Review, a Desk Reference Guide was published and is continually updated by CDER staff (last updated January 2011). GRMPs timelines are not exactly aligned with CDER's 21st Century Review timelines for all milestones. GRMPs timelines for each milestone are listed in Exhibit 2 of this report.

[4] All steps are reflected in the *FDA Guidance for Review Staff and Industry, Good Review Management Principles and Practices for PDUFA Products, April 2005.* Two milestone steps were excluded from the assessment: *Receive Application* was met by default because all cohort applications were by definition received by FDA; a second step, *Communicate Filing Determination to Applicant, if RTF*, was excluded from the assessment because only fileable applications were included in the study cohort. The GRMPs guidance does not separate Advisory Committee (AC) planning and post-meeting activities as individual milestones; however, our analysis separates out pre-AC meeting and post-AC meeting steps into five individual milestones because each are held to a unique GRMPs timeframe and could be assessed individually.

review, and the failure to meet any of these milestones should not be interpreted as a failure of the review process or FDA reviewers to conduct a thorough, quality review.

### Overall Adherence to GRMPs Milestones

For each application, GRMPs adherence was assessed based on the total number of relevant GRMPs milestones completed by the specified timeframes.[5] For the majority of GRMPs milestones, adherence was assessed based on the review team's ability to meet a timeline. In a few selected steps with no GRMPs-specific timelines, a milestone was satisfied based on completion of the step, regardless of date.[6] On average, cohort applications met 54% of applicable GRMPs milestones within the GRMPs-specified timeframe, with a range of 18% to 83%, and a median of 53%. A similar variation was observed for adherence to individual GRMPs milestones across the full study cohort, ranging from 6% to 93% of cohort applications meeting the milestone date. The milestones that were met most frequently included *Assign RPM* (90%, 55/61), *Communicate Filing Review Issues to the Applicant* (93%, 56/60), and *Take Action* (82%, 50/61). The milestones that were least frequently met included *Complete Primary Review* (6%, 4/60), as well as several Action Phase milestones such as *Draft Action Letter* (19%, 6/32), *Circulate and Review Action Package and Letter* (12%, 4/34), and sending the *Letter to Signatory Authority* (12%, 5/41).

### Adherence to Filing Determination and Planning Phase Milestones

Among the first activities performed after FDA receives an application are to assign the RPM and assemble the review team. The step to *Assign RPM*[7] was completed within the GRMPs timeframe for 90% (55/61) of cohort applications. However, only 34% (21/61) of cohort applications met the specified GRMPs timeline to complete the *Assign Review Team* activity. For 76% (32/40) of applications that did not meet this milestone, at least two discipline reviewers were assigned after the GRMPs-specified date. Timely assignments were relatively similar across disciplines, with a range from 56% (biostatistics reviewers) to 72% (facility reviewers[8]).

The primary reason for late review team assignment was that completing the administrative portion of this activity, which involved sending an e-mail to the Document Control Room staff, was a relatively low priority compared to other RPM responsibilities. Further, RPMs often did not send the notification to assign reviewers in the system until the last discipline reviewer had been selected for the application, which made the application appear in the system to have had all discipline reviewers assigned late. The reasons for the late assignment therefore appear to be administrative, rather than due to challenges with finding or selecting reviewers for an application, but this administrative delay of entering the reviewers into the system can still lead to delays in reviewers receiving application documents that are checked into the FDA system.

[5] Relevant milestones are those that are applicable to a particular application. Those that are not applicable (e.g., planning AC meeting for applications that do not require an AC meeting) were excluded from the calculation.
[6] The following steps were determined to adhere to GRMPs milestones if they were performed, regardless of completion date: *Identify Signatory Authority*, *Secondary Sign-off*, *Issue Discipline Review (DR) Letters* (as appropriate), *Plan Advisory Committee Meeting* (as needed).
[7] *Assign RPM* milestone is 14 days from application receipt date for Standard/Priority reviews; see Exhibit 2.
[8] Facility reviews pertain to BLAs and are assigned to applications in CBER.

The GRMPs milestones for *Hold Filing Meeting*[9] and *Conduct Planning Meeting*[10] were completed within the prescribed timeframes for 50% (28/56) and 52% (28/54) of cohort applications, respectively. The similarity between the two meetings is largely due to the fact that the objectives of both meetings are typically achieved in a single meeting. These meetings, when late, missed the GRMPs milestone date by an average of nine days. Scheduling conflicts were the primary reason that the filing and planning meetings were held late.

*Request Consults*[11] was performed within the GRMPs-specified timeline of 45 days upon application receipt in 23% (10/43) of cohort applications, the lowest level of adherence to GRMPs milestones among all planning phase milestones. Among those applications that missed this milestone, 67% (22/33) had more than one late consult request. Pregnancy labeling consult requests were the type most frequently late, with 11% (1/9) requested by the GRMPs milestone date. RPMs explained that many consult requests were issued after the specified timeframe because the need was difficult to predict during the first 30-45 days of the review cycle, and that there was uncertainty among the review team as to which consult requests most frequently occur as "standard consults".

*Identifying Inspection Actions*[12] was completed within the GRMPs timeframe for 29% (14/49) of applications. Based on interviews with RPMs, the appropriate reviewer identified the need for inspection actions during or shortly after the filing meeting. Since GRMPs milestones indicate that both the filing meeting and identification of inspection actions must occur within the first 45 days of application receipt, any inspections identified after the filing meeting usually fell after the GRMPs milestone date. The average amount of time by which applications missed the GRMPs milestone for this step varied by Center and by application type, with an average of 86 days late for CBER BLAs, 69 days late for CDER BLAs, and 20 days late for CDER NDAs. Some of the delays incurred for this milestone are explained by late filing meetings, however other reasons for these delays emerged from FDA survey results. Discipline reviewers often conduct an initial cursory review of the application for filing, but begin conducting a more thorough review after the filing meeting, which raises issues that were not identified previously, including inspection actions. These delays were most frequently cited as a reason for late identification of inspection actions after the 45/30 day GRMPs timeframe. Another reason why delays occurred in the identification of inspection actions is because inspection staff from the Office of Compliance (OC) reported in surveys that they are often not informed of or invited to attend the filing meeting. Infrequent attendance at the filing meeting on the part of DSI and DMPQ staff precludes opportunities for reviewers to discuss needed inspections on or before the specified GRMPs timeframe.

### Adherence to Review Phase Milestones

*Complete Primary Review* is the most significant and complex step in the course of the review, requiring the coordination and completion of application reviews among all discipline reviewers. The lowest level of adherence to GRMPs throughout the review process occurred with this step,

[9] *Hold Filing Meeting* milestone is 45/30 days from application receipt date for Standard/Priority reviews; see Exhibit 2.
[10] *Conduct Planning Meeting* milestone is 45/30 days from application receipt date for Standard/Priority reviews; see Exhibit 2.
[11] GRMPs specify consults that are considered "frequently occurring" or standard. These consult types include: Trade name/PPI, pregnancy labeling, risk, environmental assessments (EA), abuse potential, and categorical exclusions,
[12] *Identifying Inspection Actions* was assessed based on the date that any type of inspection request was submitted (Exhibit 7). GRMPs state that the milestone for this step is 45/30 days (Standard/Priority) from the application receipt date. See Exhibit 2.

where primary discipline reviews were completed on time for 6% (4/60) of cohort applications.[13] Most applications with late reviews had more than one late review discipline (96% in CDER, 82% in CBER). Among the review disciplines, the clinical review was most frequently the last to complete review (39%), which may be explained by the fact that clinical reviewers typically require input from other discipline reviews to complete the primary clinical review. Reviews that were not completed on time averaged 45-68 days late in CDER, and 38-69 days late in CBER, depending on the discipline.

The low adherence to the GRMPs for this step was most frequently attributed to a few key drivers throughout RPM interviews and discipline focus groups. The most frequently cited rationale for late primary review completion was the failure among multiple review disciplines to coordinate review completion in an efficient and timely manner. In addition, reviewers cited late completion of labeling reviews and inspections as contributing to the late completion of primary reviews. Competing workload was also cited as a factor for missing this milestone. In particular, discipline reviewers noted that their time was regularly split between multiple activities such as NDA/BLA reviews, IND reviews, unanticipated work, and special presentations. When surges in workload occurred, reviewers noted there was often insufficient capacity to complete all tasks on time.

The *Mid-cycle Meeting*[14] is the only major milestone meeting that takes place in the Review phase. Among all the major meetings, the mid-cycle meeting was described as the most important, because it provides an opportunity to assess review progress prior to the wrap-up. In CBER, mid-cycle meetings were considered the most prominent milestone because primary reviews are expected to be completed and wrap-up meetings are not uniformly held. This meeting was held within the GRMPs timeframe for 49% (20/41) of the cohort applications, which is similar to the degree of adherence of the planning and filing meetings. The late meetings were held 15 days after the milestone date on average, with a range from 1 to 52 days late. As with the other major meetings, scheduling conflicts for primary reviewers and division management were the primary reason cited for holding the meetings late.

### Adherence to Advisory Committee Phase Milestones

Adherence to GRMPs milestones varied across the five activities related to AC meetings.[15] *Planning the AC Meeting*[16] met the GRMPs milestone for all ten applications for which data on this step was obtained. There was also a relatively high degree of adherence to the GRMPs milestones for *Disclose and Disseminate Background Materials*[17] (3/5, 60%) and conducting the *Internal Meeting to Integrate AC Input*[18] (5/6, 87%). The *AC Meeting*[19] itself was conducted

[13] The GRMPs milestone for "Complete Primary Review" differs from those stated by the 21st Century Review. For GRMPs, a primary review is completed on time if completed by end of month 8/5 (standard/priority), whereas the 21st Century Review provides different completion targets if depending on whether the signatory authority is the ODE director (8/4 weeks for standard/priority) or OND division director (5/3.5 weeks for standard/priority). Also see Exhibit 2 for a summary of GRMPs timelines.
[14] *Mid-Cycle Meeting* milestone is end of month 5/3 for Standard/Priority reviews (Exhibit 2)
[15] GRMPs milestones indicate that Advisory Committee activities are performed at the end of month 8/5 (standard/priority review); however, CDER's 21st Century Review timeframes for the same activities differ (month 7-8 for a standard review, and month 4-5 for a priority review).
[16] *Planning the AC Meeting* milestone is not associated with a specific GRMPs timeframe. The milestone is met when the "need is identified", see Exhibit 2.
[17] *Disclose and Disseminate Background Materials* milestone is 2 weeks before the AC meeting date for Standard/Priority reviews, see Exhibit 2.
[18] *Internal Meeting to Integrate AC Input* milestone is 2 weeks after AC meeting for Standard/Priority reviews, see Exhibit 2.

within the GRMPs-specified timeframe 38% (6/16) of the time. On average, late AC meetings were held 38 days after the GRMPs-specified milestone date, with a range of 5 to 94 days late.

The reasons most frequently cited by RPMs for late AC meetings was difficulty in coordinating schedules, clearing attendees and finding alternates.[20] Discipline reviewers noted that the AC meeting frequently was scheduled near the end of the review cycle due to scheduling challenges, which interfered with downstream milestones such as holding a timely *Wrap-Up Meeting*[21] and *Take Action.*[22] Applications with late AC meetings were less likely to meet the PDUFA goal date to *Take Action* (4/10, 40%) than were those with AC meetings that were held on time (5/6, 83%).

### Adherence to Action Phase Milestones

The *Wrap-Up Meeting* milestone marks the transition into the Action Phase. Compared to earlier milestone meetings, a smaller proportion (36%, 14/39) of applications held wrap-up meetings on time. Late wrap-up meetings were conducted an average of 51 days after the specified timeframe, with a range of 3 to 144 days after the milestone date. Scheduling conflicts were the primary reason reported in survey findings for late wrap-up meetings, although factors such as the need for an AC meeting, lack of applicant responsiveness to requests, and incomplete meeting pre-requisites also contributed to the delays. The primary cause for the two applications with wrap-up meetings held more than 80 days late was due to major amendments issued near the time of the meeting milestone.[23]

The remaining activities in the Action phase take place in the final weeks leading up to action. The final step, *Take Action*, is one of the most consistently met milestones in the GRMPs, with 82% (50/61) of cohort applications taking action by the PDUFA goal date. By contrast, the four steps leading up to action involving the compilation, circulation and review of the action package and letter, adhered to the GRMPs milestone much less frequently. For these four steps (*Compile Action Package,*[24] *Draft Action Letter,*[25] *Circulate and Review Action Package and Letter,*[26] *and Letter to Signatory Authority*[27]) the level of adherence to GRMPs milestones ranged from 12% to 26% of applications. Among the reviews that did not complete these steps on time, these four final steps were performed on average 19 to 31 days past the GRMPs-specified timeframe, which often pushed them within days of the action date.

---

[19] *AC Meeting* milestone is end of month 8/5 for Standard/Priority reviews, see Exhibit 2.
[20] An interview with a member of the DACCM group also indicated that the competing products list required time for review teams to develop and was a source of work that competed with time to complete reviews and a potential cause of delayed AC meetings.
[21] *Wrap-up Meeting* milestone is end of month 8/5 for Standard/Priority reviews, see Exhibit 2.
[22] *Take Action* milestone is end of month 10/6 for Standard/Priority reviews, see Exhibit 2
[23] Two of the 25 late wrap-up meetings exceeded the milestone date (end of month 8) by more than 80 days (140 and 144 days). For these two applications, major amendments extended the review timeframe by three months. However, each of the major amendments was submitted by applicants after the dates that the wrap-up meetings should have been held. The two wrap-up meetings were then held only 15 days and 9 days before the extended PDUFA goal dates, which accounted for the extended delays.
[24] *Compile Action Package* milestone is 6/4 weeks before Action for Standard/Priority reviews, see Exhibit 2.
[25] *Draft Action Letter* milestone is 6/4 weeks before Action for Standard/Priority reviews, see Exhibit 2.
[26] *Circulate and Review Action Package and Letter* milestone is 6/4 weeks before Action for Standard/Priority reviews, see Exhibit 2.
[27] *Letter to Signatory Authority* milestone is 3/2/1.5 weeks before Action for Standard/Priority/ODE Director sign-off, see Exhibit 2.

The ability of review team members to initiate these final action steps is dependent on completion of primary reviews. Late completion of primary reviews, which occurred in 92% of cohort applications, compressed the timeframe available to complete final actions steps, resulting in high levels of non-compliance for initiating these activities. Only one review fully adhered to the GRMPs timelines across all four action phase steps evaluated, and primary reviews for this application were completed by the GRMPs-specified timeframe. When asked if the lead time given in GRMPs is sufficient to complete the final action milestones, 84% (16/19) of RPM interview responses indicated that the lead time indicated by GRMPs is sufficient for completing the final action steps, while a minority of RPM interview responses (16%, 3/19) indicated that this compressed timeframe presented a challenge in completing the GRMPs final action milestones. The overall view from RPM interviews and discipline reviewer focus groups was that supervisors are typically kept apprised of the review timeline through meetings, so they may require less time than the 2-3 weeks of lead time allotted by GRMPs to sufficiently review and finalize the action letter.[28]

### Booz Allen Recommendations

Booz Allen developed recommendations for process improvement by analyzing GRMPs implementation challenges described in the assessment of GRMPs compliance, and taking into account FDA and applicant process improvement suggestions that emerged through the root cause analysis. These recommendations are intended to assist FDA in making improvements to the implementation and use of GRMPs to facilitate a more efficient review process.

- **Add agenda item at mid-cycle meeting for disciplines to discuss and coordinate necessary review inputs –** The most frequently cited rationale for why primary reviews were not completed on time was the failure among multiple review disciplines to coordinate review completion in an efficient and timely manner. Mapping of review interdependencies among disciplines revealed that all disciplines are dependent at times on at least one other discipline to complete their primary reviews. However, clinical reviews have the highest number of and strongest level of dependencies on the inputs from all other discipline reviews. A mid-cycle meeting agenda that includes an item for each discipline to note required inputs would promote early coordination and initiation of any communication plans needed to share information to complete primary reviews. Drafts or near-complete versions of reviews could be planned for exchange between discipline reviewers, so that primary reviews across disciplines may be completed on or before the GRMPs milestone date.

- **Identify standard consults –** RPMs and discipline reviewers noted ambiguity in identifying necessary consults for an application review. Center-wide identification during training of a clear set of “standard”, frequently occurring consults could eliminate delays during the early part of a review cycle to issue needed consults. The potential benefits of identifying “standard” consults is to increase the number of consult requests that could be initiated by RPMs within the first 45 days of the review, thereby affording consult reviewers longer lead-time to perform reviews. FDA survey findings revealed that the labeling/Patient Package Insert (PPI) consult was the only consult type that most reviewers agreed upon as predictably or frequently occurring. However, Office of Surveillance and Epidemiology (OSE) labeling reviewers (i.e., Division of Medication Error Prevention and Analysis (DMEPA), Division of Risk Management (DRISK)) report

[28] To validate these conclusions from RPMs and discipline reviewers, interviews will be conducted with Division Directors in upcoming weeks.

that they are often not invited to or informed of filing meetings and infrequently attend, so the need for labeling reviews is often determined late. Inclusion of labeling reviewers at the filing meeting could facilitate timely identification of needed consults. In addition, an electronic dropdown menu or checklist in FDA systems of all available consult types, including an open text box area in the checklist, could allow RPMs to quickly check off needed consults, add in any specific application-specific directions in a free-type text box, and automatically notify consult reviewers of requests. Such functionality could decrease the time and effort needed to generate consult requests on the part of RPMs, and could streamline the process needed to promptly notify appropriate consult reviewers.

- **Emphasize timely milestone meetings in training** – Failure to hold timely major meetings was in part due to the belief among most RPMs and discipline reviewers that meeting milestones need not be strictly interpreted. Training on GRMPs that heightens awareness of and emphasizes the importance of timely meetings, most notably at mid-cycle and wrap-up, could aid team collaboration efforts. Emphasis on timely meetings, combined with adequate meeting preparation on the part of discipline reviewers and RPMs, would relieve work compression closer to the action date and ensure that meetings are productive.

- **Provide on-demand GRMPs training to CDER and CBER review staff –** GRMPs training has been developed by FDA to educate review staff on GRMPs milestones. Many CDER RPMs referred to formal training received from the 21st Century Review, and other RPMs reported learning about GRMPs through informal meetings and mentorship, and could not recall more specific training courses on GRMPs. A GRMPs training and refresher course that is widely implemented across CDER and CBER could set a stronger baseline understanding of all GRMPs milestones among review staff. FDA survey findings revealed a strong interest among CDER and CBER staff to participate in a training or refresher course on GRMPs, and a belief that the course would have utility in improving adherence to milestones. Review staff also remarked that training would be most helpful if made available online or as a searchable reference to allow real-time, on-demand access to materials.

- **Update NDA/BLA submission guidance for industry –** On average, applications in the study cohort failed to adhere to approximately 50% of milestone steps. Aside from late completion of primary reviews, many RPMs interviewed identified missing applicant data in the original submission as a key issue impacting compliance with these final action steps. One potential solution is to update existing draft and final guidances on the NDA/BLA submission process, including standard elements and content examples necessary for a complete application, in an effort to align existing guidances with the current FDA views on submissions. Applicants interviewed commented that updated guidances would aid them in the submission process. Another benefit to FDA and applicants include minimizing incomplete application submissions and the need for a large number of information requests. Due to the effort required to update guidances, an immediate next step could be to prioritize guidances that could be updated, either through identification of the most outdated guidances or to determine their perceived utility to applicants.

- **Use Refuse to File (RTF) authority more effectively –** In addition to assisting applicants with more current guidance, another potential solution is for the FDA review team to conduct a more thorough review early in the review cycle to identify missing data

components by the filing meeting. Any deficiencies identified in data submissions could result in increased usage of RTF for incomplete applications and improve the quality of applications that undergo a complete review cycle. An RTF Manual of Policies and Procedures (MaPP) is currently in development by CDER that could assist review teams in determining the types of application deficiencies that could trigger RTF decisions.

- **Provide specific timeframes for responses to information requests –** Missing applicant data could also be addressed if FDA issues specific timeframes on information requests (IRs) to applicants. Applicant interviews indicated that clearer guidance on timeframes for expected responses would allow applicants to gauge the level of urgency with which responses should be submitted to FDA, and could improve FDA's ability to anticipate submission of missing data and coordinate review, especially near the end of the review cycle.

- **Initiate identification of inspection actions prior to application filing –** Office of Compliance (OC) staff at CDER indicated in survey responses that earlier identification and communication of necessary domestic and foreign manufacturing and clinical inspection actions prior to filing would improve timely completion of inspections. A consolidated and comprehensive list of inspection sites could be requested from applicants during clinical studies and/or at the pre-submission meetings, and potentially included as an agenda item for discussion (e.g., End-of-Phase 2 meetings, pre-NDA/BLA meetings) so that FDA may identify potential domestic and foreign facilities for inspections prior to application filing for planning purposes. Early and consistent notification and inclusion of OC representatives at pre-submission meetings and early identification and submission of site information prior to NDA/BLA submission could extend the timeframe that OC would have available to schedule and complete timely inspections after submission, especially for priority review applications that require foreign inspections to be performed. In addition, automating applicant submission of manufacturing and clinical site information so that it may be readily accessible to OC could also speed and improve the accuracy by which sites are identified and selected for inspections. Applicants also indicated that late awareness and notification of requested inspections by FDA is a likely contributor to late scheduling and completion of inspections. Earlier engagement with and notification of manufacturers of necessary inspections would enable companies with variable production cycles to better anticipate and improve coordination of active production cycles, and permit FDA inspections to be more promptly scheduled and conducted.

- **Develop team assignment roster form** – Review team assignment dates currently entered into IT systems often do not accurately reflect the date that the reviewer is selected for the review team. Development and implementation of a team assignment roster form that is consistently used and completed by RPMs at the beginning of the review cycle to include all review discipline team member names (e.g., OC, OSE) and assignment dates could improve the accuracy and reliability of this documentation going forward. Keeping a roster could serve as a reminder to the RPM of unfilled team assignments. In addition, this would enable the correct review team members to be identified if application inquiries are necessary, serve as a comprehensive list to remind RPMs of all team members who should be selected to participate in meetings and have access to submission materials, and improve the accuracy of future Center or Division assessments of GRMPs implementation.

# 2. TASK BACKGROUND AND OBJECTIVES

Under the 2002 Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures, FDA agreed to meet specific performance goals.[29] Under Goal X of the PDUFA III goals (First Cycle Review Performance Proposal), FDA agreed to create a joint guidance for review staff and industry on good review management principles and practices (GRMPs) that apply to the first cycle review of New Drug Applications (NDAs), Biologics License Applications (BLAs) and efficacy supplements.[30] The GRMPs clarify the roles and responsibilities of review staff in managing the review process and identify ways in which NDA and BLA applicants may enhance the effectiveness and efficiency of the review process. The PDUFA III goals also specified that training must be provided to FDA staff in association with the implementation of GRMPs.

The implementation of the Food and Drug Administration Amendments Act of 2007 (FDAAA) created new review activities to be completed within the review cycle, such as determining the need for and developing postmarketing requirements (PMRs) and Risk Evaluation and Mitigation Strategies (REMS). The 2007 PDUFA Reauthorization Performance Goals and Procedures[31] expanded the implementation of GRMPs. Under Goal X of the PDUFA IV goals (First Cycle Review Performance Proposal), FDA agreed to further enhancements associated with notifying applicants in the Filing Communication letter of the anticipated timeline for review of the application, including the anticipated date for initiation of discussions regarding product labeling and any FDA requirements for postmarketing study requirements (PMRs) or requests for postmarketing study commitments (PMCs).

The GRMPs are intended to improve the effectiveness and efficiency of the first cycle review of new product applications. During the first review cycle, a well-managed review process allows sufficient time for careful regulatory decision-making, and if needed, time to work with the applicant to resolve readily correctable deficiencies in the application. For applications that otherwise meet the standards for approval, the process allows for finishing the review of the labeling and other regulatory issues (e.g., development of PMRs/PMCs and REMS) and issuance of an approval letter on or before the PDUFA goal date, thereby eliminating unnecessary, inefficient additional review cycles. However, if FDA uncovers substantial deficiencies during an application's first cycle review or an applicant does not respond to requests for information in a timely manner, then additional review cycles may be necessary to address all deficiencies in an application. Such a well-managed review process fulfills FDA's public health mission to make safe and effective products available to the public in a manner that is timely, while making the most efficient use of the Agency's limited resources.

Under the PDUFA III goals, Booz Allen conducted an evaluation of first cycle reviews of NDAs for new molecular entities (NMEs) and BLAs submitted in FY 2002 through 2004, which included a study of the impact of the GRMPs.[32] A second Booz Allen study was a prospective study of first cycle reviews for NMEs and original BLA submissions starting in FY 2005 and

[29] See 2002 PDUFA Reauthorization Performance Goals and Procedures - http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html
[30] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf
[31] http://www.fda.gov/oc/pdufa4/pdufa4goals.html
[32] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119469.htm

continuing through FY 2007.[33] The GRMPs were not fully implemented by the end of PDUFA III and could not be fully evaluated in the PDUFA III independent evaluation. Also PDUFA IV provided for additional enhancements to the GRMPs as described above. Therefore, the PDUFA IV goals require an independent assessment of the progress toward full implementation of the GRMPs, focusing on both FDA reviewer practices and industry applicant practices affecting successful implementation.

The key objective of this task is to assess the progress of CDER and CBER in fully implementing GRMPs including the PDUFA IV enhancements focusing on both FDA reviewer practices and industry applicant practices affecting successful implementation. Once the degree of GRMPs implementation was established, a root cause analysis to examine underlying factors that promote or inhibit successful GRMPs implementation was conducted. Root cause analysis is a systematic approach to identify contributors to efficient process implementation. This approach advances the study beyond determining GRMPs implementation and the timeliness of implementation to identifying motivating behaviors and characteristics that facilitate or impede compliance. By directing recommendations and corrective measures at root causes, it is hoped that the likelihood of problem recurrence will be minimized in the future.

To achieve this objective, this assessment consisted of the following activities:

- Determine the degree of current implementation of GRMPs by review divisions in CDER and CBER, including the parts of the GRMPs that divisions were already using before the promulgation and implementation of the GRMPs.
- Conduct a root-cause analysis to identify the main obstacles and enablers impacting GRMPs implementation.
- Recommend actions that would improve the effectiveness of the GRMPs implementation.

It is important to note that this study did not, and was not intended to, evaluate the quality of the review, the scientific and medical evaluation, or the technical merit of the review decision. The array of activities and associated milestones in the GRMPs constitutes an important element of improving the effectiveness and efficiency of the NDA/BLA review process. However, these milestones are intended as guidelines in the process to facilitate the management of a timely review, and the failure to meet any of these milestones should not be interpreted as a failure of the review process or FDA reviewers to conduct a thorough, quality review.

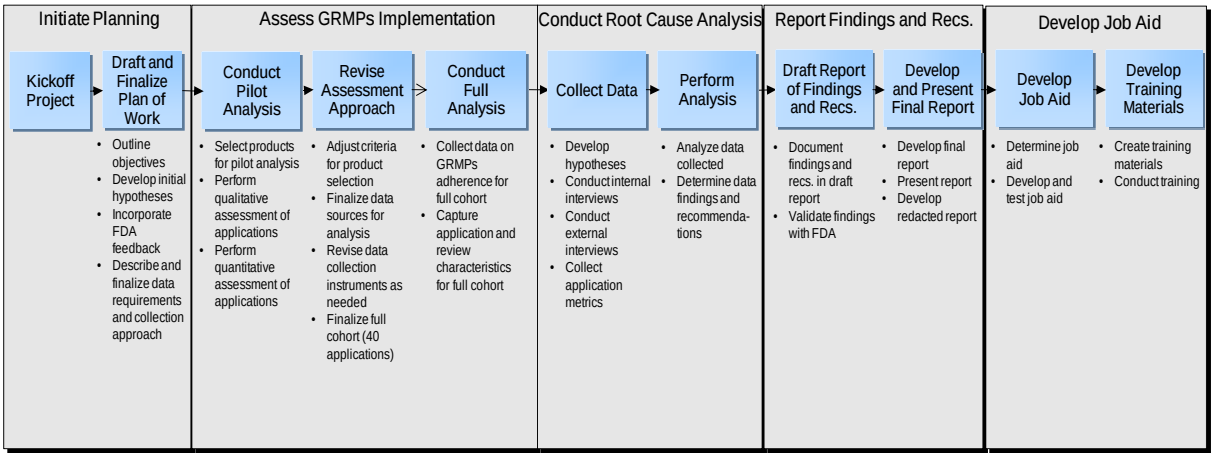
The methodology used to assess implementation of GRMPs and assessment of root cause is described in the following section.

[33] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm127117.htm

# 3. METHODOLOGY

The task consists of five phases, as illustrated in Exhibit 1, which provides an overview of the overall technical approach. The final step of the project, developing the job aid and training materials, will take place after the completion of this report.

**Exhibit 1. High Level Technical Approach**




The task consists of five phases as described below.

1. **Initiate Planning:** In the first phase, initial hypotheses were developed and data requirements were identified by evaluating the overall GRMPs activities.

2. **Assess GRMPs Implementation:** In the second phase, the degree of GRMPs implementation by review divisions was determined by collecting data on GRMPs compliance for a selected product cohort. The level of GRMPs implementation was assessed using existing documentation in FDA data systems and document archives. A brief RPM survey was also used to fill gaps in the documentation.

3. **Conduct Root Cause Analysis:** The third phase focused on identification of root causes for lack of adherence to GRMPs. Inputs for the root cause analysis were derived from conducting one-on-one interviews with RPMs, holding focus groups, and conducting applicant interviews. Findings from the root cause analysis were then validated through an FDA survey that was administered online to review staff in CDER and CBER.

4. **Report Findings and Recommendations:** In the fourth phase, initial findings and recommendations based on the GRMPs data collection, RPM interviews and focus groups were submitted in a draft report for FDA review and feedback. The final report incorporates additional insights and feedback from FDA CDER and CBER representatives.

5. **Develop Job Aid:** The final phase of the project will entail development and implementation of a job aid/tool to assist supervisors and managers in implementing recommendations with their employees.

The detailed methodology for each of these phases of work is described in Sections 3.1 to 3.5.

The GRMPs process consists of five major phases comprising 42 activities, as described in the GRMPs Guidance for Review Staff and Industry.[34] This process, as well as applicable GRMPs-specified timeframes for completion of each milestone for standard and priority reviews, is illustrated at a high level in Exhibit 2.

**Exhibit 2. GRMPs Major Process Activities and Timelines**

| **GRMPs Activity**[35] | **Timeline Standard** | **Timeline Priority** |
|---|---|---|
| **Filing Determination and Review Planning Phase** | | |
| * Receive Application[36] | Day 0 | Day 0 |
| 1. Assign RPM | Day 14 | Day 14 |
| 2. Begin Regulatory Filing Review | Day 14 | Day 14 |
| 3. Acknowledge Application Receipt in Writing | Day 14 | Day 14 |
| 4. Assign Review Team[37] | Day 14 | Day 14 |
| 5. Applicant Orientation Presentation (optional) | Day 45 | Day 30 |
| 6. Designate Priority Review | Day 45 | Day 30 |
| 7. Conduct Filing Review | Day 45 | Day 30 |
| 8. Convey Potential Refuse to File (RTF) Issues to Applicant | Day 45 | Day 30 |
| 9. Hold Filing Meeting | Day 45 | Day 30 |
| 10. Request Consults (most frequently used) | Day 45 | Day 30 |
| 11. Identify Inspection Actions | Day 45 | Day 30 |
| 12. Identify Signatory Authority | Day 45 | Day 30 |
| 13. Make Filing Decision | Day 45 | Day 30 |
| 14. Conduct Planning Meeting | Day 45 | Day 30 |
| 15. Inform Applicant of a Priority Designation in Writing | N/A | Day 60 |
| 16. Communicate Filing Determination to Applicant, if RTF[38] | Day 60 | Day 60 |
| 17. Communicate Filing Review Issues to Applicant | Day 74 | Day 74 |
| **18. Include PDUFA IV enhancements in Filing Communication (anticipated review timeline including dates for initiation of discussions about labeling and PMRs/PMCs)** | Day 74 | Day 74 |
| **Review Phase** | | |
| Conduct Review[39] | Begin when assigned | Begin when assigned |
| 19. Mid-Cycle Meeting | End of Month 5 | End of Month 3 |
| 20. Complete Primary Review | End of Month 8 | End of Month 5 |
| 21. Secondary Sign-Off/Review | Variable | Variable |
| 22. Issue DR Letters, as appropriate | Variable | Variable |
| **23. Send REMS notification letter to sponsor**[40] | Variable | Variable |

[34] These steps are reflected in the *FDA Guidance for Review Staff and Industry, Good Review Management Principles and Practices for PDUFA Products, April 2005.*
[35] All bolded steps are evaluated as part of PDUFA IV enhancements.
[36] This step is assumed rather than assessed in this evaluation, since applications must have been received by FDA and completed first cycle review to be included in the study cohort.
[37] For this evaluation, the review team includes the RPM, clinical reviewer, non-clinical reviewer, clinical pharmacology reviewer, biometrics reviewer, product quality reviewer. Safety RPM and OSE RPM are assigned to the review team later in the review cycle, so were not evaluated for adherence to this milestone.
[38] For this evaluation, this step was not assessed, as only completed first cycle reviews were selected in the study cohort (i.e., no RTF applications).
[39] This step is a GRMPs activity without a specific milestone date; since it cannot be measured, the step was not assessed in the study.

| GRMPs Activity | Timeline Standard | Timeline Priority |
|---|---|---|
| **Advisory Committee Meeting Phase** | | |
| 24. Plan Advisory Committee (AC) Meeting | When need is identified | When need is identified |
| 25. Disseminate and disclose applicant and FDA background materials | 2 weeks before AC meeting | 2 weeks before AC meeting |
| 26. Conduct AC Meeting | End of Month 8 | End of Month 5 |
| 27. Internal meeting to integrate AC input | 2 weeks after AC meeting | 2 weeks after AC meeting |
| 28. Confidential memo to AC to announce action | At action | At action |
| **Action Phase** | | |
| 29. Wrap-Up Meeting | End of Month 8 | End of Month 5 |
| 30. Internal Briefings for Signatory Authority (as needed) | End of Month 8 | End of Month 5 |
| 31. Preapproval Safety Conference (for NMEs in CDER) | 4 weeks before approval | 4 weeks before approval |
| 32. Initiate Compliance Check Request (BLAs) | 4 weeks before approval | 4 weeks before approval |
| **33. Labeling Discussions (for Approval Actions) begun by target date set in 74 day letter (PDUFA IV), except in cases where labeling will not be included in the action** | 3 weeks before sign-off or date specified in filing communication | 3 weeks before sign-off or date specified in filing communication |
| **34. Negotiation of PMRs/PMCs, if needed and begun by the target date set in 74 day letter (PDUFA IV)** | 3 weeks before sign-off or date specified in filing communication | 3 weeks before sign-off or date specified in filing communication |
| 35. Negotiation of Risk Management Program, if needed, including REMS | 3 weeks before sign-off | 3 weeks before sign-off |
| 36. Compile Action Package | 6 weeks before action | 4 weeks before action |
| 37. Draft Action Letter with Conditions for Approval or List of Deficiencies (for complete response) | 6 weeks before action | 4 weeks before action (3 weeks – 21st Century Review) |
| 38. Circulate and Review Action Package and Letter | 6 weeks before action | 4 weeks before action (3 weeks – 21st Century Review) |
| 39. Letter to Signatory Authority | 3 weeks before action | 2 weeks before action (1.5 weeks if ODE Director sign-off) |
| 40. Action | End of Month 10 | End of Month 6 |
| **Post-Action Phase** | | |
| 41. Conduct Lessons Learned (Post-action feedback meeting) | After PDUFA goal date | After PDUFA goal date |
| 42. Clarify Deficiencies and Expected Outcomes (End of Review Conference) | After PDUFA goal date | After PDUFA goal date |

The assessment of GRMPs adherence strictly assessed whether each GRMPs milestone was met before or on the indicated timeframe.

## 3.1. Initiate Planning

During the planning phase, Booz Allen developed a plan of work that outlined project activities and objectives, presented hypotheses regarding GRMPs adherence and developed data collection approaches and requirements. An initial plan was developed during this phase for collecting data and identifying the data sources. Data sources for this task included

[40] A REMS notification letter is not a GRMPs activity, but is part of the development process for REMS, which were established in FDAAA.

document/literature reviews, database queries, and interviews with FDA reviewers and applicants. Booz Allen also determined initial criteria for selection of applications to be analyzed in the GRMPs assessment, as shown in Exhibit 3. The applications in the study consisted of those that had reached first-cycle action within the previous 12 months,[41] to ensure that the assessment would provide a recent snapshot of current practices and the degree of implementation. A list of candidate applications was identified by running the appropriate searches and report queries in FDA data systems, and the final cohort selection was made during the next project phase.

**Exhibit 3. GRMPs Assessment Cohort Selection Criteria**

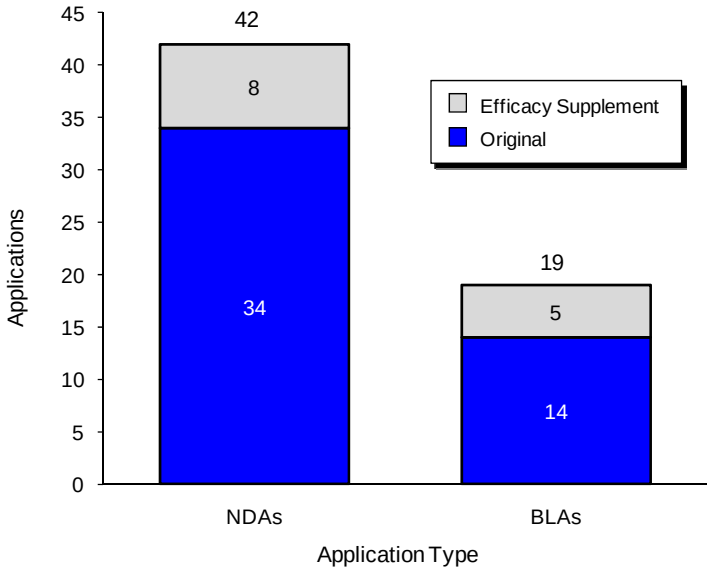
| Category | Selection Factor |
|---|---|
| Center/Division Characteristics | • Applications from both CDER and CBER<br>• Two applications from each review division or review office |
| Product Characteristics | • BLAs and NDAs<br>• Original applications and efficacy supplements<br>• NME and non-NME<br>• Variety of disease indications |
| Review Characteristics | • Priority and standard review<br>• Approval and Complete Response actions<br>• Normal and accelerated approval<br>• Applications with and without AC meeting<br>• Applications with and without REMS with Elements to Assure Safe Use (ETASU)<br>• Applications with and without PMRs/PMCs<br>• Review completed within last 12 months |
| Applicant Characteristics | • Large and small applicant-submitted applications (note: applicant size determined by market capitalization at time of submission) |

## 3.2. Assess GRMPs Implementation

Booz Allen conducted a pilot study in the initial data collection and analysis phase of the project to validate the data collection plan and address potential data gaps before initiating the full study. In consultation with the project's Technical Advisory Group (TAG), eight applications were selected (two from CBER and six from CDER) from a variety of review divisions and offices to assess GRMPs compliance. After collecting and analyzing the lessons learned from the pilot study, Booz Allen made revisions to the data collection plan to address data gaps. The full study cohort ("the cohort") for the GRMPs assessment consisted of 48 original applications (34 NME NDAs and 14 BLAs) and 13 supplement applications (8 NDAs and 5 BLAs) that were received in FY09 (October 1, 2008 – September 30, 2009) and reached first cycle action within a recent 12-month timeframe (August, 2009 – July, 2010). The cohort included applications submitted to and reviewed by both CDER (49 applications) and CBER (12 applications), with a mixture of priority and standard reviews. The cohort also included applications with a mixture of original and efficacy supplements, NMEs and non-NME products, and Approval and Complete Response first cycle actions. Exhibit 4 depicts an overview of the full study cohort.

[41] The timeline was determined at project kickoff to include applications receiving first cycle action between August 2009 and July 2010.

**Exhibit 4. Full Product Cohort for the GRMPs Assessment**




Each review division and office within CDER and CBER was represented in the cohort. A detailed list of cohort applications and their characteristics is available for reference in Appendix A.

As illustrated in Exhibit 5, a variety of other product characteristics were taken into account during application selection to ensure diversity of the study cohort. One of the characteristics measured was first cycle action. In the cohort, 49% (30/61) of applications selected were approved in the first cycle, and of these approved applications, 33% (10/30) were BLAs. The criteria described in Exhibit 3 during the Planning phase were taken into consideration when finalizing the GRMPs study cohort.

**Exhibit 5. Other Review Characteristics of Full GRMPs Study Cohort**

| Other Review Characteristics | First Cycle Action | | NME/Non-NME | | | Priority Classification | | Advisory Committee | | REMS ± ETASU | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | AP | CR | NME | Non-NME | Supple-ment | Priority | Standard | Yes | No | Yes | No |
| **NDAs** | 48% (20) | 52% (22) | 33% (14) | 48% (20) | 19% (8) | 31% (13) | 69% (29) | 26% (11) | 74% (31) | 19% (8) | 81% (34) |
| **BLAs** | 53% (10) | 47% (9) | 74% (14) | 0% (0) | 26% (5) | 32% (6) | 68% (13) | 21% (5) | 63% (14) | 26% (5) | 74% (14) |

Booz Allen captured data using the data collection instrument (DCI) developed during the pilot study and identified any issues or concerns encountered with the process. Booz Allen collected input on the degree of implementation of GRMPs by analyzing data available on FDA data systems first. Information was captured and recorded in the DCI in a comprehensive assessment to include not only GRMPs-specific information, but also broader categories of data specific to each application. Data were gathered on:

- FDA and applicant characteristics (e.g., Office, Division, applicant size)

- General product characteristics (e.g., indication, orphan designation)
- Application characteristics (e.g., Standard vs. Priority status, data on REMS and PMRs)
- Submission quality and review communication characteristics (e.g., type and quantity of amendments and information requests, labeling submissions, the use of filing checklists)

An overview of the types of data collected in the DCI and the sources used to obtain that data are presented in Exhibit 6. A detailed description of the data sources and specific criteria used to analyze key GRMP activities with low adherence is presented in Exhibit 7. FDA data systems, FDA documents (including electronic and hard copy action packages), FDA internal communications, and external communications to applicants served as the primary source for basic information on product and application characteristics (e.g., priority/standard review designation, Advisory Committee meeting, number of amendments submitted, approval or complete response action). These data were analyzed and hypotheses were developed regarding the explanation for either failure or success in complying with (i.e., adhering to) the GRMPs milestones. Booz Allen applied strict timelines for evaluating adherence to each milestone as outlined by the GRMPs guidance. For example, to be considered adhering to the GRMPs step *Completion of Primary Reviews* for a given application, all key discipline reviews (including clinical, non-clinical, clinical pharmacology, biostatistics, and product quality) must have submitted a completed draft of their reviews, obtained secondary sign-off either from a team leader or supervisor, and logged these reviews into the appropriate FDA data system by the end of month 8 (end of month 5 for Priority review). An application that contained even one discipline review completed and submitted after the GRMPs-specified timeframe was considered not to have adhered to the GRMPs for that step. After capturing application and review characteristic data for the full cohort, a root cause analysis was performed as described in the following section.

**Exhibit 6. Overview of Data Sources Used in the GRMPs Assessment**

| Category | Sample Characteristics | Data Sources |
|---|---|---|
| Basic Information | • Application number and type<br>• Product name and applicant<br>• Submission and action dates<br>• Action outcome | • FDA data systems |
| Center/Division Characteristics | • Review Center/Division | • FDA data systems |
| Applicant Characteristics | • Applicant size (market cap)<br>• Applicant experience | • Internet search<br>• Orange Book |
| Product Characteristics | • Original or supplement<br>• NME/Non-NME, first in class status<br>• Orphan status<br>• Product indication<br>• Unmet need | • FDA data systems<br>• Internet search |
| Application Characteristics | • Priority or standard<br>• Accelerated approval, Fast Track<br>• REMS with ETASU<br>• PMRs/PMCs, FDAAA PMRs<br>• AC Meeting held | • FDA data systems<br>• Hard copy<br>• RPM checklist |

| Category | Sample Characteristics | Data Sources |
|---|---|---|
| Submission Quality and Review Characteristics | • Pre-submission meeting held<br>• Number of IRs and amendments<br>• Communication of submission timelines<br>• Use of review and action checklists | • FDA data systems<br>• Hard copy<br>• RPM questionnaire |

An overview of data sources for each major analysis is shown in Exhibit 7. This table is not inclusive of all steps in the assessment, but highlights the detailed sources and the criteria used to assess adherence to GRMPs milestones for key steps in the analysis that were identified to have low adherence and are the focus of the descriptive analysis in the following sections.

**Exhibit 7. Data Sources and Criteria Used to Assess GRMPs Adherence**

| GRMPs Milestone | Data Source | Method Used to Assess Adherence to GRMPs |
|---|---|---|
| **Assign Review Team** | • FDA data systems | • Review team summary pages provided reviewer names and corresponding dates logged into FDA system |
| | • Filing Meeting Date (CDER, CBER)<br>• First Committee Meeting Date (CBER) | • Reviewer names and corresponding dates if reviewer was present at meeting |
| | • Filing Checklist (CDER) | • Reviewer assignment dates |
| **Hold Timely Meetings** | • FDA data systems<br>o Filing Checklists<br>o Action Package Checklists<br>o LAR Checklists | • Dates for filing/planning meetings are typically indicated in these checklists<br>• Date stamps in meeting minutes available through IT systems |
| | • RPM Survey | • Dates for mid-cycle meetings, wrap-up meetings, and pre-approval safety conferences |
| **Request Inspection Actions** | • FDA data systems<br>o DSI Consult Requests<br>o Review Team Communications Documents that indicate clinical or manufacturing requests | • Dates of inspection actions logged into FDA data systems (with the exception of EES) |
| | • RPM Survey | • Dates for this milestone if unavailable through FDA data systems |
| **Initiate Compliance Check Requests** | • FDA data systems<br>o Compliance Check Request Forms<br>o Review Team Communications Documents | • Dates logged into CBER data system or date stamps from e-mail or other written communications |
| | • RPM Survey | • Dates for this milestone if unavailable through data systems |
| **Complete Primary Reviews** | • FDA data systems<br>o Primary Discipline Reviews<br>o Action Package Checklists | • All key discipline reviews (clinical, non-clinical, clin/pharm, biostatistics, and product quality) must have: 1) submitted a completed draft of their reviews; 2) obtained secondary sign-off from a team leader or supervisor; 3) logged reviews into IT systems by the end of month 8 (end of month 5 for Priority status).<br>• Applications with one or more reviews submitted after the GRMPs specified timeframe was considered non-compliant<br>• Sign-off dates in hard copy action packages, or dates as available through action package checklists |
| | • Hard Copy Action Packages | • Dates signed off on paper documents when electronic copies were unavailable |
| **Advisory Committee Meeting** | • FDA data systems<br>o RPM Filing Review<br>o RPM Action Package<br>o CDTL Clinical Summary<br>o Pre-Approval Safety Conference Memo | • Clinical review summaries and other sources logged into IT systems |
| | • RPM Survey | • Dates provided by RPMs for all AC steps (highly dependent on RPM records) |
| | • FDA-Sponsor Communications | • Emails and telecon minutes between FDA and sponsor |
| | • AC Calendar (FDA website) | • AC meeting agendas/summaries logged into AC Calendar on FDA website |
| | • RPM Interviews | • Dates provided by RPMs |
| **Final Action Steps** | • FDA data systems | • Date final action letter was signed by the signatory authority |
| | • RPM Survey | • Dates provided by RPMs for all final steps: Compile action package, Draft letter to review team, Circulate letter and action package, Signatory Authority sign-off |

## 3.3. Conduct Root Cause Analysis

Booz Allen conducted a root cause analysis to investigate the underlying factors that contribute to successful GRMPs implementation. This assessment advanced the study beyond determining the degree and timeliness of GRMPs implementation to identifying motivating behaviors and characteristics that facilitate or impede adherence. Data on each application for the root cause analysis were gathered from FDA documents, RPM interviews, discipline reviewer focus groups, applicant interviews, and FDA validation surveys. Targeted interviews were conducted with 33 RPMs who were involved with the review of the cohort applications, using a structured interview guide to collect additional information to test the root cause hypotheses. Focus groups were held with a total of 48 different reviewers across ten different review disciplines (five in CDER and five in CBER). For the root cause analysis, Booz Allen conducted one-hour interviews with RPMs to fill in missing data gaps and to determine enablers and barriers to GRMPs adherence. A similar method was used in the one-hour focus groups with review teams to gather additional data and identify underlying drivers for failure to comply with GRMPs milestones. Complementary approaches were used to select participants for product-based interviews and focus groups, as depicted in Appendix C. Interviews were conducted with RPMs because they were responsible for meeting the majority of the GRMPs steps and could identify application-specific reasons for non-adherence. Focus group discussions were held with discipline reviewers to address a fewer number of GRMPs steps in order to ascertain a broader perspective on non-adherence. A survey was also administered more broadly to FDA review staff to refine initial findings from RPM interviews and discipline reviewer focus groups. Interviews were also conducted with representatives of industry applicant companies to further refine the findings and obtain the applicant's perspective on the GRMPs process and the planned review timelines. A detailed description of the root cause analysis data collection process follows:

- **RPM interviews** were held to identify the underlying drivers affecting GRMPs adherence, current review process challenges and process improvement opportunities. Booz Allen convened 33 interviews of RPMs who managed the review of different NDAs/BLAs in our study product cohort. A copy of the RPM discussion guide is included in Appendix B.

- **Discipline reviewer focus groups** were held to identify the underlying drivers affecting GRMPs adherence, current review process challenges and process improvement opportunities. Booz Allen convened ten focus groups consisting of two to eight review team members within the same discipline who had reviewed different NDAs/BLAs in both CDER and CBER. Each of the focus group types, number of participants, and focus group discussion guide are shown in Appendix C.

- **Industry applicant interviews** were conducted to assess issues affecting successful implementation of GRMPs in applications submitted to each review division within both CBER and CDER. Booz Allen convened 13 interviews of applicants selected from among the study's cohort applications. The applicant's perspective provided useful input on the implementation and impact of the GRMPs on the review process, as well as suggestions on how to improve the review process in general. FDA requested that the Agency remain blinded to applicants that participated in the GRMPs study to encourage candid responses from applicants and to ensure confidentiality of information provided. General applicant characteristics and the interview guide used to conduct the telephone interviews are summarized in Appendix D.

- **FDA staff surveys** were developed to refine and further validate preliminary findings and key themes that emerged from the study's initial phases of evaluation. The surveys were administered online in January 2011 to discipline reviewers, RPMs, and supervisors/team leaders at CDER and CBER, with a total of 409 respondents (122 CBER, 287 CDER). Customized online surveys were also developed for Office of Compliance (OC) participants (24 respondents) and Office of Surveillance and Epidemiology (OSE) staff (17 respondents). Survey participant characteristics and FDA survey questions are included in Appendix E.

## 3.4. Report Findings and Recommendations

The GRMPs compliance assessment and root cause analysis culminated in the development of this final report, which includes results of all analyses and proposed recommendations. The analyses were quantitative (including frequency analysis of qualitative data) and GRMPs adherence was assessed for each application in the cohort by calculating available data for each step depicted in Exhibit 2. Adherence was determined based on a strict interpretation of GRMPs timelines for each step (e.g., if an application missed the milestone date for *Hold Filing Meeting* by one day, it was still considered late). Data points collected through various sources were calculated in the DCI where possible to determine whether the application had adhered or not adhered to the GRMPs for each step. In certain cases, data was unavailable or could not be calculated and was designated as "Not Applicable." Percent adherence was tabulated by dividing the number of compliant applications per step by the total number of compliant and non-compliant applications.[42]

The recommendations are qualitative in nature based on the root cause analysis findings. Booz Allen used a systematic approach to determine the underlying factors that contributed to lack of adherence to GRMPs milestones. Responses to questions from structured interview guides, facilitated one-on-one telephone discussions with RPMs and applicants, and focus groups with discipline reviewers were aggregated in a data collection sheet. Frequency analyses were conducted to quantify FDA review staff responses to online survey questions and were used to support qualitative recommendations. Overarching themes were identified from these data analysis methods as root causes for either failure to adhere to GRMPs milestones or underlying factors contributing to adherence with GRMPs based on the most frequently occurring responses. Our approach with interviews involved asking follow-on questions to probe and identify the root causes of the problems.

Findings include review processes, behaviors and dynamics of organizational culture that promote or inhibit adherence to GRMPs milestones. Recommendations highlight potential areas of improvement, and suggestions as to potential process changes that could provide the most value to the review team.

## 3.5. Develop Job Aid

Booz Allen will work with FDA to implement solutions aimed at improving adherence to GRMPs timeframes and overall review efficiency. If appropriate, this may include developing a job-aid, as well as creating appropriate training materials and training sessions, to assist review team staff in increasing adherence to GRMPs milestones. Development of the job-aid concept, tool, and accompanying documentation will be based upon prioritization of recommendations

[42] Applications for which a step was "Not Applicable" were not included in calculating percent adherence.

resulting from findings of the root-cause analysis, and specific requirements of the job-aid will follow based on discussions with FDA.

### 3.5.1. Develop Job Aid

Based on analysis of study findings, Booz Allen will identify job aids that would best support FDA review staff in meeting GRMPs milestones. Interviews with review team staff will provide feedback on procedural or cultural factors that detract from staff ability to meet designated timelines, as well as review team perceptions on the availability, utility, and gaps of current tools (e.g., guidance, checklists, and templates).

After identifying areas where a job aid might help address or mitigate factors contributing to failure to adhere to GRMPs timeframes, Booz Allen will work with the TAG to develop and prioritize concepts for potential job aids that could be created for staff use. Based on feedback, we will develop an initial version of the job aid to pilot on a sample of representative users, which may include review team staff from a variety of disciplines and roles across CBER/CDER, or depending on staff needs and tool design, to target for use by certain functional roles (e.g., RPMs).

### 3.5.2. Develop Training Materials

Once the job aid is ready for testing, training materials will be developed and a meeting or demonstration session will be conducted to explain the purpose and benefits of the tool, and how to use it. We will incorporate any feedback from attendees on the job aid to make further refinements to its content and format, ensure 508-compliance, and finalize any user guides, presentations, or media required to support roll-out of the job aid.

# 4. FINDINGS

Based on methodology described above, findings are reported on the evaluation of adherence to GRMPs milestones using primary and secondary data sources. This section organizes the study's findings into the following subsections:

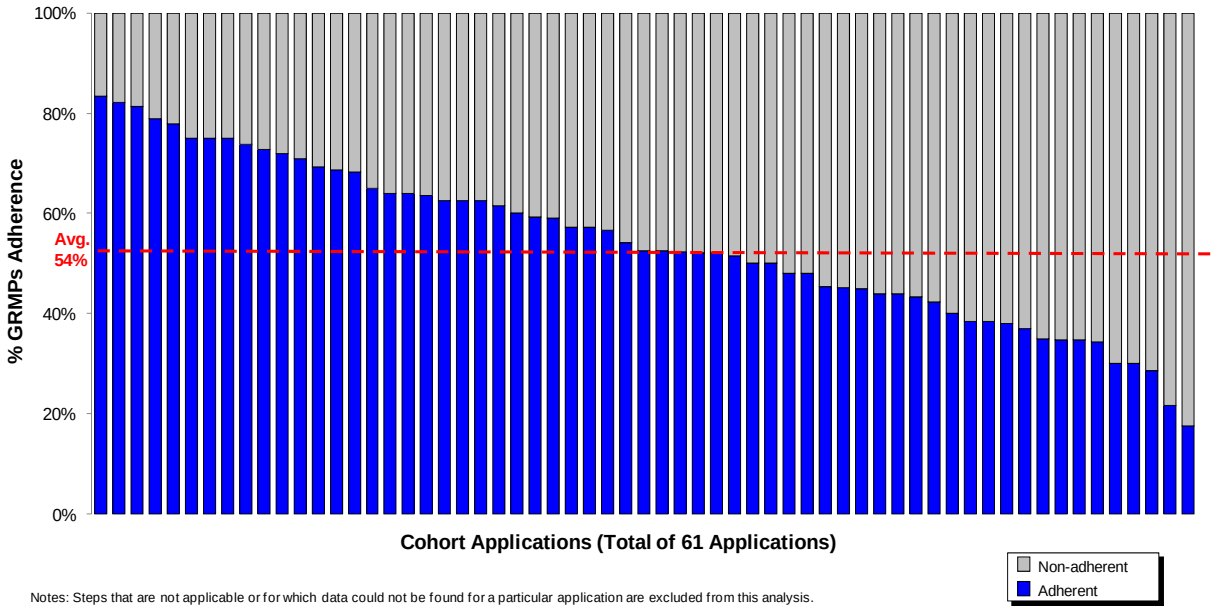
- Findings related to overall adherence to the GRMPs milestones for the aggregate study cohort
- Detailed findings for adherence to GRMPs milestones for specific steps within each GRMPs review phase

The detailed findings for each review phase include descriptions of the selected milestone steps, adherence levels across the application cohort, and discussion of root causes behind non-adherence to GRMPs milestones.

## 4.1. Adherence to GRMPs Milestones

Adherence to GRMPs milestones was assessed individually for each application in the selected cohort. The timelines for all GRMPs milestones assessed in the study are summarized in Exhibit 2. The number of GRMPs milestones that were applicable to each review and the number of data points that were available for each milestone application differed for each application, ranging from 10 to 31 milestones. For each application, GRMPs adherence was assessed based on the total number of relevant GRMPs milestones, and depicted in Exhibit 8**.** On average, cohort applications performed 54% of applicable GRMPs milestones within the specified timeframe, ranging from a low of 18% (3/17 applicable steps) to a high of 83% (15/18 applicable steps), and a median of 53% (10/19 applicable steps). All applications in the cohort missed at least three GRMPs milestones.

**Exhibit 8. Adherence to GRMPs Milestones by Individual Application**




Notes: Steps that are not applicable or for which data could not be found for a particular application are excluded from this analysis.

While all GRMPs steps were performed to some degree, the level of adherence to GRMPs-specified timeframes varies widely between GRMPs milestones. Exhibit 9 provides a summary of the degree of adherence to each GRMPs milestone that is associated with a fixed timeline based on the applications analyzed in the product cohort.[43]

The milestones that met GRMPs-specified timeframes most frequently were:

- *Assign RPM (90%)*[44]
- *Communicate Filing Review Issues to the Applicant (93%)*[45]
- *Take Action (82%)*[46]
- *Identify Signatory Authority (100%)*[47]
- *Secondary Signoff (100%)*[48]

[43] Five GRMPs milestones, which are considered optional, conducted on an as-needed basis, or otherwise lack a specified GRMPs timeframe, could not be assessed for adherence and were excluded from this summary exhibit, including step 5) Applicant Orientation Presentation (optional), step 22) Issue DR Letters (as needed), step 30) Internal Briefings with Signatory Authority (as needed), step 41) Conduct Lessons Learned (optional), and step 42) Clarify Deficiencies and Expected Outcomes (optional).
[44] *Assign RPM* milestone is 14 days from application receipt date for Standard/Priority reviews (Exhibit 2).
[45] *Communicate Filing Review Issues to the Applicant* milestone is 74 days from application receipt date for Standard/Priority reviews (Exhibit 2).
[46] *Take Action* milestone is end of month 10/6 for Standard/Priority reviews (Exhibit 2).
[47] *Identify Signatory Authority* milestone is 45/30 days from application receipt date for Standard/Priority reviews. (Exhibit 2).
[48] The *Secondary Signoff* milestone is variable, with no specific GRMPs timeframe (Exhibit 2). Therefore, any primary review that has received secondary signoff is considered to be compliant with GRMPs.

Assigning the RPM is the first step in the review, while taking action is the last step in the review, so most reviews begin and end on time. *Communicate Filing Review Issues to the Applicant* (74-day letter) is considered by RPMs to be an important planning phase step and is consistently sent to applicants on time. The signatory authority is usually the Office Director or Division Director, and is generally determined by the chemical classification of the application, except in special circumstances. Unless otherwise noted in documentation, this step was assumed to have taken place by the appropriate milestone (100%). Another step that always adhered to the GRMPs (100%) was *Secondary Signoff*, which is a necessary component of completing a primary review.[49] This step is not associated with a specific GRMPs timeline; thus, all application reviews that received secondary signoff prior to the PDUFA goal date were considered compliant for this step.

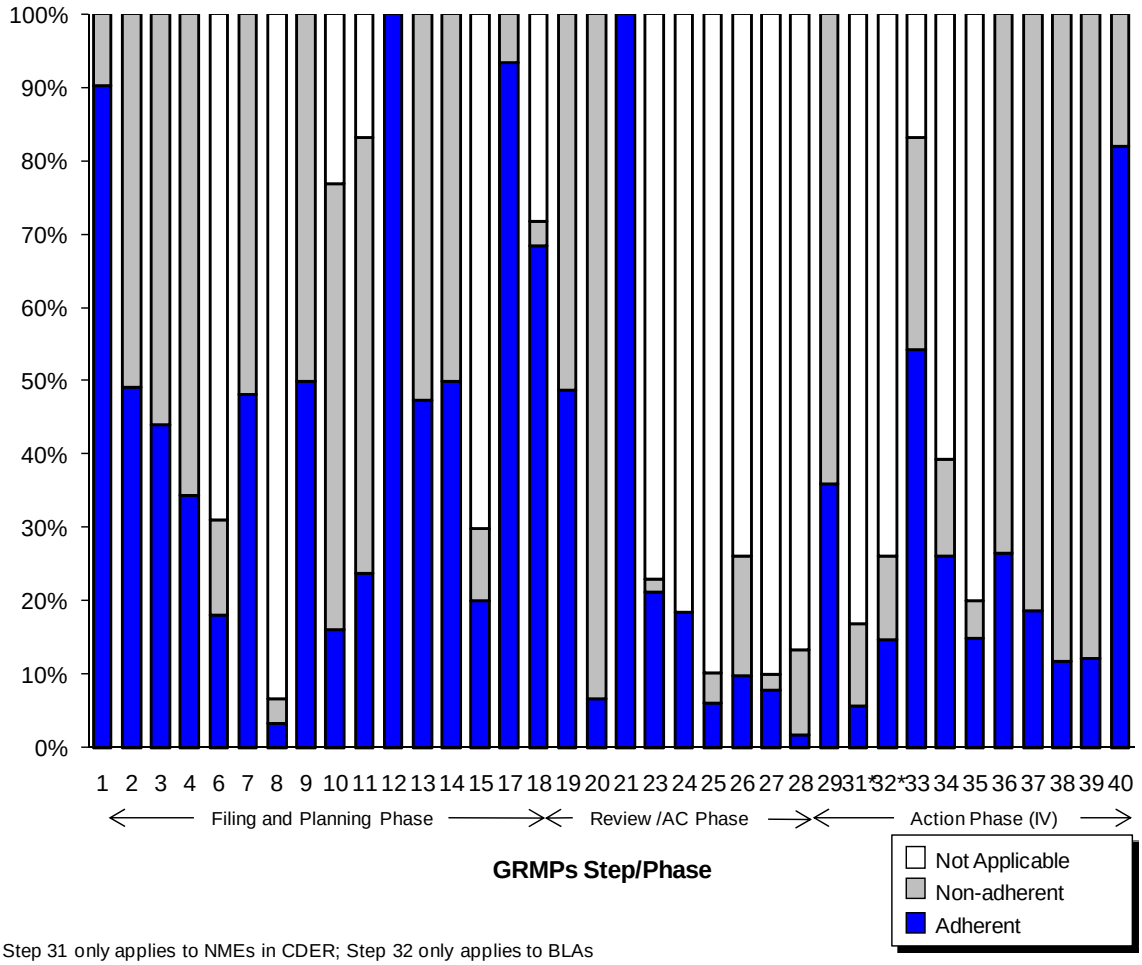
By contrast, the milestones that were least frequently met are grouped into a number of process categories, including:

- Internal review requests: *Request Consults* (22%)[50] and *Identify Inspection Actions* (28%)[51]
- Major meetings: *Conduct Advisory Committee Meeting* (37%)[52] and *Wrap-up Meeting* (36%)[53]
- *Complete Primary Review* (6%)[54]
- Final steps leading up to final action: *Compile Action Package* (26%),[55] *Draft Action Letter* (19%),[56] *Circulate and Review Action Package and Letter* (12%),[57] and *Letter to Signatory Authority* (12%).[58]

Milestones for which the GRMPs-specified timeframes were consistently missed across the application cohort were identified for further analysis, so that factors contributing to low adherence could be determined. These GRMPs milestones are the focus of subsequent analysis and described in detail in Sections 4.2-4.5.

[49] The milestone *Secondary Signoff,* is considered met (GRMPs-compliant) if a secondary reviewer has affixed a signature to the completed review, or written a separate summary review.
[50] *Request Consults* milestone is 45/30 days from application receipt date for Standard/Priority reviews. (Exhibit 2).
[51] *Identify Inspection Actions* milestone is 45/30 days from application receipt date for Standard/Priority reviews. (Exhibit 2).
[52] *Conduct Advisory Committee Meeting* milestone is end of month 8/5 for Standard/Priority reviews. (Exhibit 2).
[53] *Wrap-up Meeting* milestone is end of month 8/5 for Standard/Priority reviews. (Exhibit 2).
[54] *Complete Primary Review* milestone is end of month 8/5 for Standard/Priority reviews. (Exhibit 2).
[55] *Compile Action Package* milestone is 6/4 weeks before Action for Standard/Priority reviews. (Exhibit 2).
[56] *Draft Action Letter* milestone is 6/4 weeks before Action for Standard/Priority reviews. (Exhibit 2).
[57] *Circulate and Review Action Package and Letter* milestone is 6/4 weeks before Action for Standard/Priority reviews. (Exhibit 2).
[58] *Letter to Signatory Authority* milestone is 3/2/1.5 weeks before Action for Standard/Priority/ODE Director sign-off. (Exhibit 2).

**Exhibit 9. Adherence to GRMPs Milestones for Fixed Timelines**




* Step 31 only applies to NMEs in CDER; Step 32 only applies to BLAs
Note: Five steps that are optional and/or not associated with fixed GRMPs timelines are excluded: 5) Applicant Orientation Presentation (Optional), 22) Issue Discipline Review Letters (as appropriate), 30) Internal Briefings to Signatory Authority (as needed), 41) Conduct Lessons Learned, 42) Clarify Deficiencies and Expected Outcomes.

**GRMPs Step/Phase**

Filing and Planning Phase (I)
1. Assign RPM
2. Begin Regulatory Filing Review
3. Acknowledge Application Receipt in Writing
4. Assign Review Team
6. Designate Priority Review
7. Complete Filing Review
8. Convey Potential RTF Issues to Applicant
9. Hold Filing Meeting
10. Request Consults (most frequently used)
11. Identify Inspection Actions
12. Identify Signatory Authority
13. Make Filing Decision
14. Conduct Planning Meeting
15. Inform Applicant of a Priority Designation in Writing
16. Communicate Filing Determination to Applicant, if RTF
17. Communicate Filing Review Issues to Applicant
18. Include PDUFA IV Enhancements in Filing Communication

Review (II)/AC Phase (III)*
19. Mid-Cycle Meeting
20. Complete Primary Review
21. Secondary Sign-Off
23. Send REMS Notification Letter to Sponsor
24. Plan Advisory Committee (AC) Meeting
25. Disseminate & disclose applicant/FDA background materials
26. Conduct AC Meeting
27. Internal meeting to integrate AC input
28. Confidential memo to AC to announce action
29. Wrap up Meeting
31. Preapproval Safety Conference (for NMEs in CDER)
32. Initiate Compliance Check Request (BLAs)

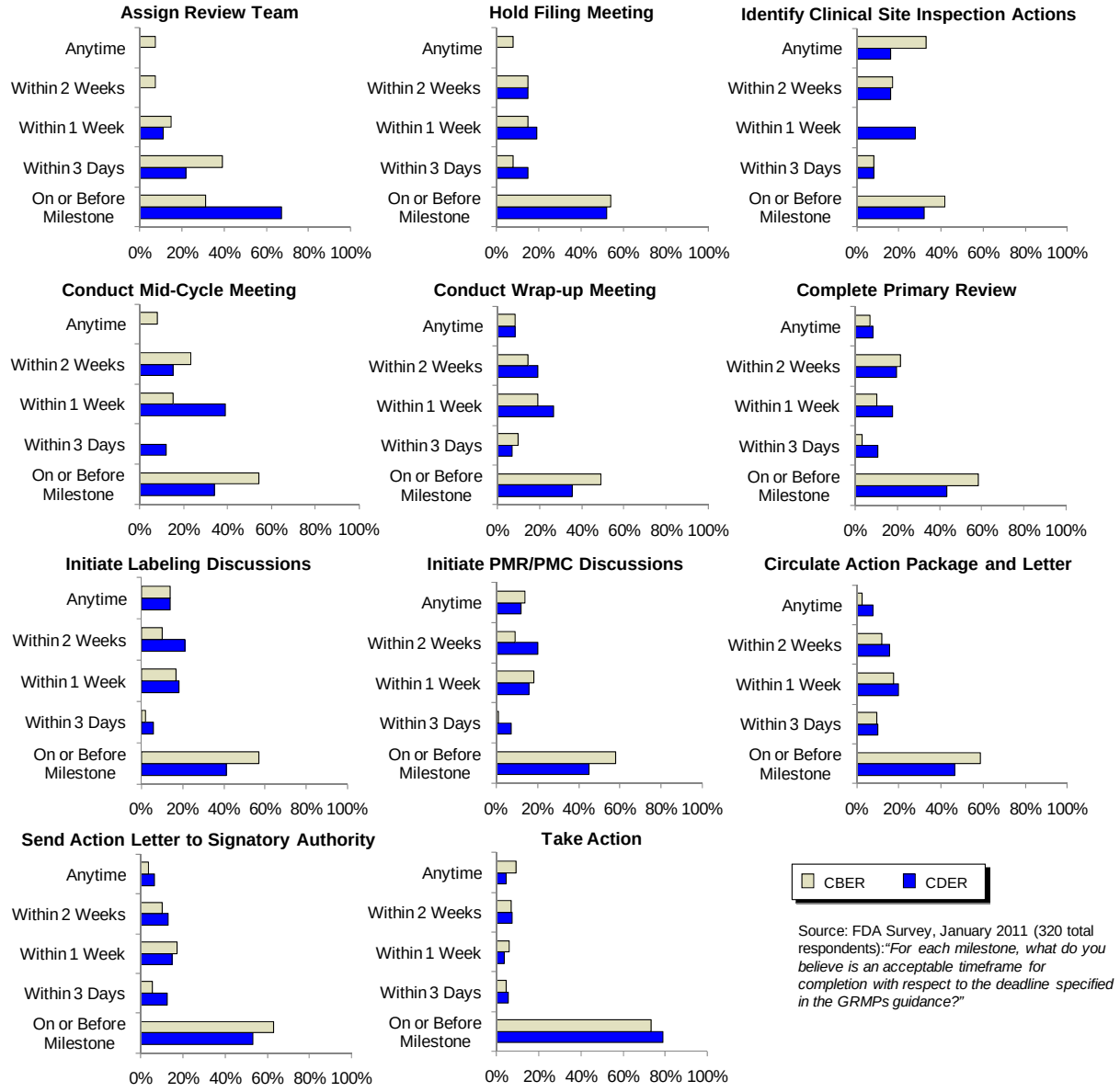
Action Phase (IV)
33. Labeling Discussions (for Approval Actions)
34. Negotiate PMRs/PMCs
35. Negotiate Risk Management Plan
36. Compile Action Package
37. Draft Action Letter with Conditions for Approval or List of Deficiencies
38. Circulate and Review Action Package and Letter
39. Letter to Signatory Authority
40. Action

While Booz Allen applied strict timelines to evaluate adherence to each milestone as outlined by the GRMPs guidance, FDA staff perceptions of acceptable timeframes for completion varied across milestones, based on responses to the FDA survey. For example, a large proportion of CDER and CBER review staff perceived that the *Take Action* step should be completed promptly on or before the milestone date (CDER: 79%, CBER 73%), as compared with other steps, such as *Identify Clinical Site Inspections* (CDER: 32%, CBER: 42%), as shown in Exhibit 10. While only a small percentage[59] of review staff believed that these steps could be completed anytime during the review process, at least one-third of FDA review staff believed that completion of these steps within one to two weeks of the GRMPs-specified timeframes was acceptable.

The levels of GRMPs adherence to specific milestones, which is detailed in the following sections, generally correlate with current FDA staff perceptions of acceptable timeframes for milestone completion. For example, adherence to GRMPs timeframes for major meetings was 50% for the *Hold Filing Meeting* (28/56), 49% (20/41) for *Mid-Cycle Meeting*, and 36% (14/39) for *Wrap-up Meeting*. The average number of days late for non-adherent meetings increased for each major meeting type held later in the review cycle. On average, filing meetings were held 9 days late, while the average delay in mid-cycle meetings and wrap-up meetings was by 15 days and 51 days. Similarly, a higher proportion of FDA staff indicated that completion of steps within one to two weeks of the milestone was acceptable for the mid-cycle meeting (38-54%) and wrap-up meeting (33-45%) than compared to the filing meeting (30-34%). For the *Take Action* milestone, the majority of CBER (73%) and CDER (79%) staff responded that the step should be completed on or before the GRMPs milestone, which correlates with the level of GRMPs adherence to this step (82%).

[59] Percentage responses that an acceptable completion timeframe is “Anytime” during the review cycle ranged from 8% to 15% for steps listed in Exhibit 10, with the exception of one milestone, *Identify Inspection Actions,* for which 33% of CBER respondents stated that “Anytime” was acceptable to complete this step.

**Exhibit 10. FDA Staff Perceptions of Acceptable Timeframes for Completion of Selected GRMPs Milestones**



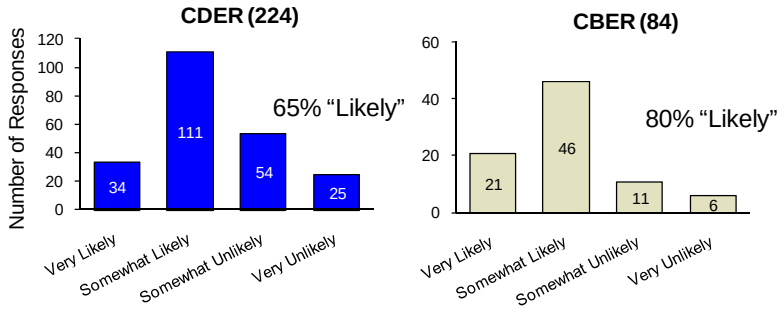

Source: FDA Survey, January 2011 (320 total respondents):*"For each milestone, what do you believe is an acceptable timeframe for completion with respect to the deadline specified in the GRMPs guidance?"*

Since the time that GRMPs were developed, a training course was developed and implemented by FDA to educate FDA review staff on the GRMPs milestones. Many CDER RPMs referred to formal training received from the 21st Century Review, which incorporated GRMPs milestones, while other RPMs reported learning about GRMPs through informal meetings and mentorship, and could not recall more specific training courses on GRMPs. In contrast, CBER currently manages BLA reviews through its Managed Review Process,[60] which is designed to meet PDUFA performance measures and backlog goals. While the Managed Review Process includes a subset of GRMPs activities and milestones, GRMPs are generally not closely aligned

[60] CBER's Managed Review Process is organized in three phases to correspond with the biologic product development lifecycle, including pre-submission/investigational, application/supplement (marketing), and post-marketing phases.

with CBER's current process and do not appear to be systematically tracked.[61] FDA survey findings of review staff in both CDER and CBER revealed a strong interest among staff to participate in training or refresher courses on GRMPs, and a belief that the course would have utility in improving adherence to milestones (Exhibit 11). However, a higher proportion of CBER respondents perceived that training or resources on GRMPs would likely improve adherence to milestones than in CDER, which could be due to the fact that CDER already has a well-developed training program in place for the 21st Century Review, and that GRMPs are not formally operationalized at CBER.

**Exhibit 11. Perceived Likelihood of Training to Improve GRMPs Adherence**




Source: FDA Survey, January 2011. *"How Likely Would Refresher Training Improve GRMPs Compliance?"*

## 4.2. Detailed Findings for Selected Planning Phase Milestones

Milestones for which FDA review teams experienced the most significant challenges in adhering to GRMPs milestones and had the greatest potential impact on the review process are discussed below.

### 4.2.1. Assign Review Team

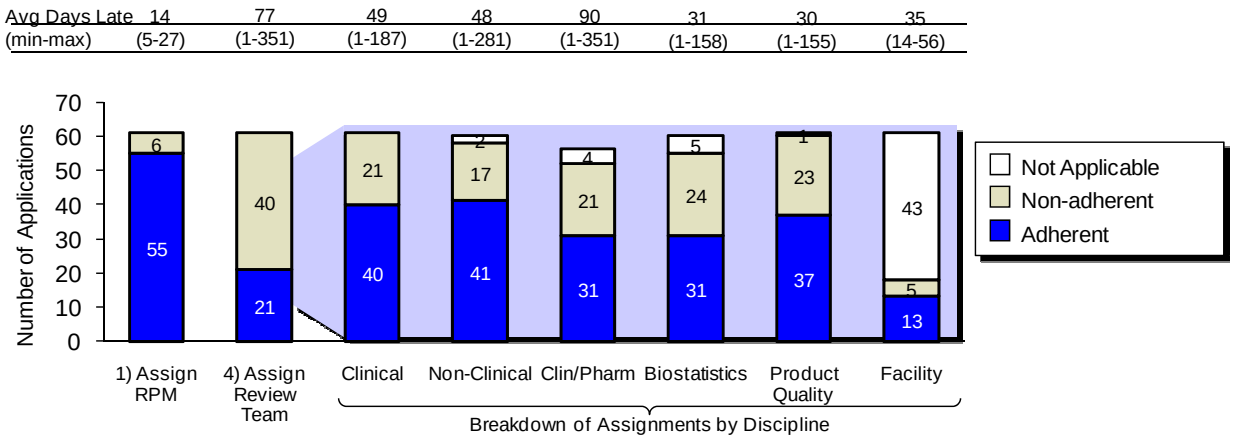
In the planning phase, 34% (21/61) of cohort applications met the specified GRMPs timeline for the early planning step, *Assign Review Team*, which is indicated to occur within the first 14 days of application receipt by FDA. This is in contrast to the milestone *Assign RPM*, which met the same specified GRMPs timeline in 90% (55/61) of cohort applications. Since GRMPs adherence for review team assignment usually requires assessing more than one assignment date for multiple members of a review team, the criteria used to determine adherence for review team assignment was based on the date the last discipline reviewer was assigned to the review team. Disciplines assessed for review team assignment dates included clinical, non-clinical (i.e., pharmacology/toxicology), clinical pharmacology, biostatistics, product quality, and facility (only for BLAs) reviewers. Adherence with the review team assignment step required that all disciplines listed above to be logged into FDA data systems or indicated through proxy documents, with assignment dates falling within the 14-day period.

Exhibit 12 illustrates adherence levels of the application cohort with the steps *Assign RPM* and *Assign Review Team*, as well as the timeliness of assigning each individual review discipline. On-time assignments of individual review disciplines ranged from 56% (31/55) for biostatistics

[61] CBER formally tracks measured milestones in FDA data systems. Of these measured milestones, 8/11 overlap with GRMPs, but these only represent a subset of the 42 GRMPs milestones assessed in this study.

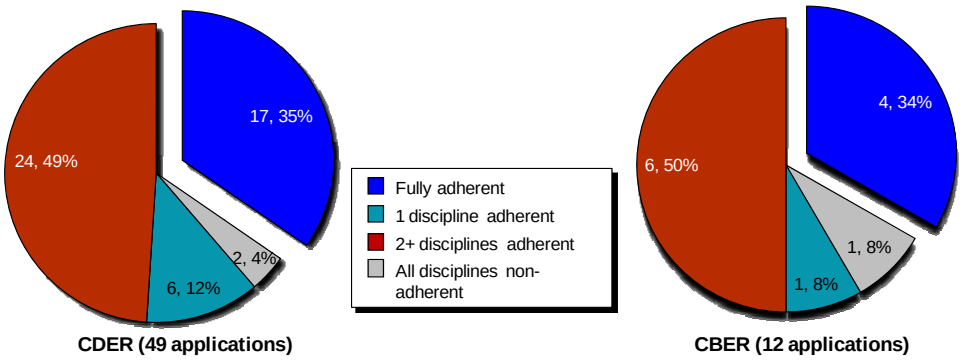
reviewers to 72% (13/18) for facility reviewers[62]. The low adherence with assigning the review team on time was comparable across CDER and CBER, with at least one application from each CDER and CBER review division missing the GRMPs timeline for review team assignment.

**Exhibit 12. GRMPs Adherence for Assigning Review Team Members**




Further analysis of the *Assign Review Team* step indicated that among reviews that did not adhere to the GRMPs milestone, 70% of applications overall involved two or more late review disciplines. Exhibit 13 illustrates GRMPs adherence based on the number of review disciplines that were assigned on a timely basis for CDER and CBER. At least one review discipline was assigned late in 65% of CDER (32/49) and 67% of CBER (8/12) applications.

**Exhibit 13. GRMPs Adherence by Total Number of Review Disciplines Assigned to Review Team**




The root cause of non-adherence with review team assignment is largely due to the relatively low priority of this step compared to other administrative activities associated with the start of a new application review. In interviews, 15 RPMs reported possible reasons for late review team assignments. For example, RPMs responded during interviews that review team members are often identified in advance of an NDA/BLA submission because many of the same review team members performed earlier-stage reviews of the same product (e.g., IND submission, SPA, or

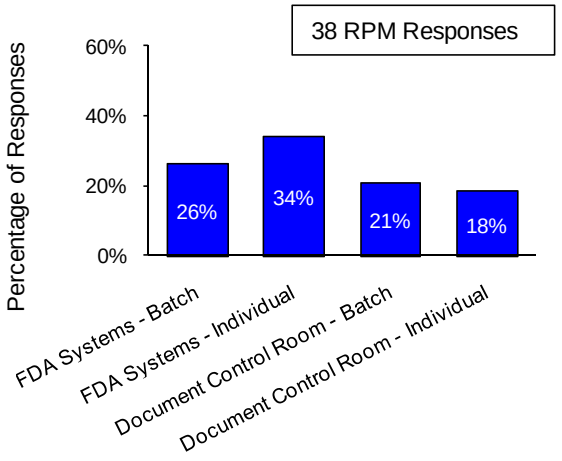
[62] Facility reviewers are logged into FDA systems for CBER BLAs; however, facility reviewers are not logged into FDA systems for CDER NDAs; therefore in Exhibit 12 there is a larger number of applications for which facility reviewer assignments are "not applicable".

pre-NDA or pre-BLA submission meetings). However, due to the relatively low priority of this step, RPMs commented that they may not promptly log review team members into FDA systems or delay communication of review team assignments to the Document Control Room, which logs review team assignments into the systems.

RPMs commonly delegate the electronic logging of review team assignments to the Document Control Room. Among RPMs who use this practice, typically only a list of review team member names is sent in an email. While RPMs reported that Document Control Room staff was responsive and prompt in logging review team members into FDA data systems, Document Control Room staff used the date stamp of the RPM's e-mail as the review assignment date, rather than the actual dates of review team assignment, which are not usually included in RPM e-mails to the Document Control Room.

Approximately half of surveyed RPMs wait until all review team members are assigned before requesting the Document Control Room to enter assignments or before they directly enter team assignments into electronic systems. The remaining half of RPMs uses the Document Control Room or directly enters each team member into electronic systems individually, as soon as each member is assigned. Exhibit 14 represents the different methods used by CDER RPMs to complete this GRMPs milestone step.

**Exhibit 14. CDER RPM Methods of Assigning Review Team**




Source: FDA Survey, January 2011: *Question to RPMs: "How do you typically assign the review team?"*
Note: "Batch" refers to sending all review team assignments at once; "Individual" refers to sending review team assignments singly

Due to differences in administrative practices such as those illustrated in Exhibit 14, the dates currently logged into FDA systems may not accurately reflect actual team assignment dates. Further analysis of alternative artifacts, such as meeting minutes, filing checklists, and reviews, revealed that reviewer assignments were made earlier than indicated in FDA systems.

### 4.2.2. Hold Timely Meetings

Adherence to GRMPs for planning phase meeting milestones (*Hold Filing Meeting*[63] and *Conduct Planning Meeting*[64]) ranged from 33% to 52%. Three other meetings take place later

[63] *Hold Filing Meeting* milestone is 45/30 days from application receipt date for Standard/Priority reviews. (Exhibit 2).

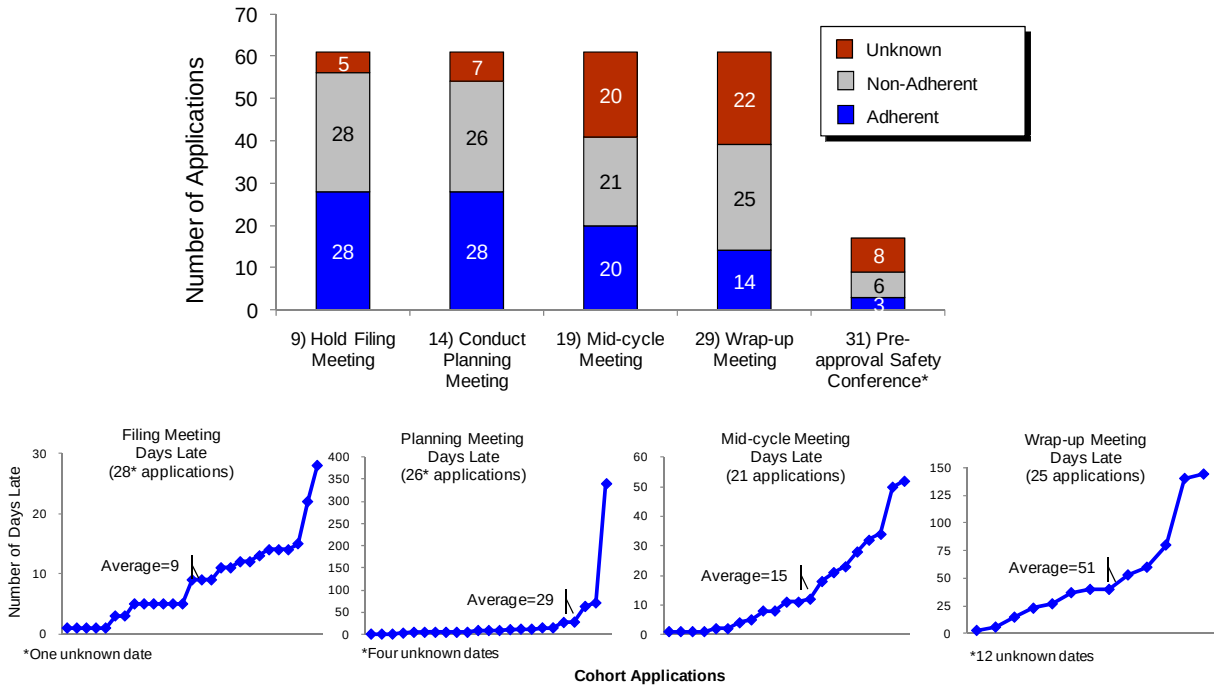
during the review and action phases (*Mid-cycle Meeting,*[65] *Wrap-up Meeting,*[66] and *Pre-approval Safety Conference*[67]), and adherence to milestones for these steps is discussed here in the context of CDER's and CBER's overall adherence in holding timely meetings over the course of an application review cycle.

Adherence to GRMPs timeframes for major meetings was 50% for filing (28/56) and planning meetings (28/54), 49% (20/41) for mid-cycle meetings, and 36% (14/39) for wrap-up meetings (Exhibit 15). Adherence was defined as completing the meeting by the specified GRMPs timeframe, with no grace period. Adherence within seven days after the GRMPs timeframe was 73% for filing (41/56) and 70% for planning meetings (38/54), 68% (28/41) for mid-cycle meetings, and 41% (16/39) for wrap-up meetings. While the planning meeting and filing meeting are listed separately in GRMPs milestones, the planning and filing meetings are frequently combined in practice.

Thirty-six percent (14/39) of cohort applications with available data for this step held wrap-up meetings on time as part of the standard review. Discipline reviewers indicated that while wrap-up meetings occur regularly for CDER reviews, they are usually not held in CBER. In CBER, the discussion of final review issues takes place during the mid-cycle meeting for reviews. Fewer cohort applications held separate pre-approval safety conferences (NMEs only), because the discussion of safety issues was incorporated in the wrap-up meeting.

[64] *Conduct Planning Meeting* milestone is 45/30 days from application receipt date for Standard/Priority reviews. (Exhibit 2).
[65] *Mid-Cycle Meeting* milestone is end of month 5/3 for Standard/Priority reviews. (Exhibit 2).
[66] *Wrap-up Meeting* milestone is end of month 8/5 for Standard/Priority reviews. (Exhibit 2).
[67] *Pre-approval Safety Conference* milestone is 4 weeks before action. (Exhibit 2).

**Exhibit 15. GRMPs Adherence for Key Meetings**




* Few separate Pre-approval Safety Conferences were held for NMEs, as this step is often combined with the Wrap-up Meeting

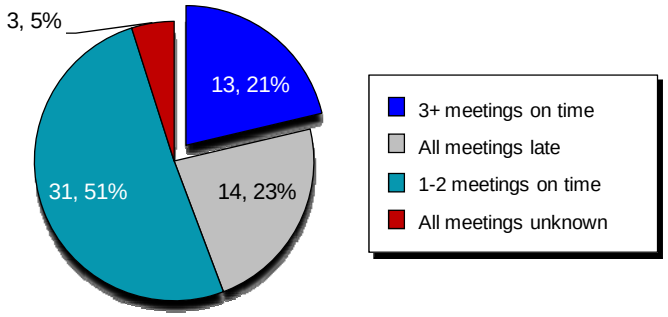
Note: Filing meeting and planning meeting dates are the same in 36 applications. Adherence indicates that the meeting was held within the GRMPs-specified timeframes.

When held late, the filing meeting was on average nine days late (min/max of 1 to 28 days, N=28), while the mid-cycle meeting was held an average of 15 days late (min/max of 1 to 52 days, N=21), and late wrap-up meetings were conducted an average of 51 days after the specified timeframe (min/max of 3 to 144 days, N=13[68]).

Only 21% (13/61) of reviews adhered to GRMPs timeframes for three or more major meetings. Reviews with adherence to GRMPs timeframes for three or more meetings were associated with higher overall adherence to GRMPs milestones, such as *Assign Review Team*, *Identify Inspection Actions*, *Complete Primary Review,* and *Take Action* (Exhibit 16).

[68] 25 applications were not adherent to GRMPs timeframes; however, exact dates were provided for 13 of these applications.

**Exhibit 16. GRMPs Adherence Across Meeting Types**




| Compliance of selected GRMPs steps | 4) Assign Review Team | 11) Identify Inspection Actions | 20) Complete Primary Review | 40) Take Action |
|---|---|---|---|---|
| 3+ meetings on time | 54% (7/13) | 55% (6/13*) | 18% (2/13) | 92% (12/13) |
| All meetings late | 21% (3/14) | 10% (1/14**) | 0% (0/14) | 79% (11/14) |

* For 2 applications, dates for identifying inspection actions were unknown; thus, adherence was calculated based on known values (6/11)

** For 4 applications, identification of inspection actions was not applicable; thus, adherence was calculated based on applicable values (1/10)

Major meetings were cited as important and informative by RPMs and discipline reviewers. Of the major meetings, the mid-cycle meeting was noted as most important. In CDER, mid-cycle meetings were used as an opportunity to assess review progress prior to the wrap-up. In CBER, mid-cycle meetings were the most prominent milestone because substantial progress on primary reviews was expected to be made by that point and wrap-up meetings were not uniformly held.

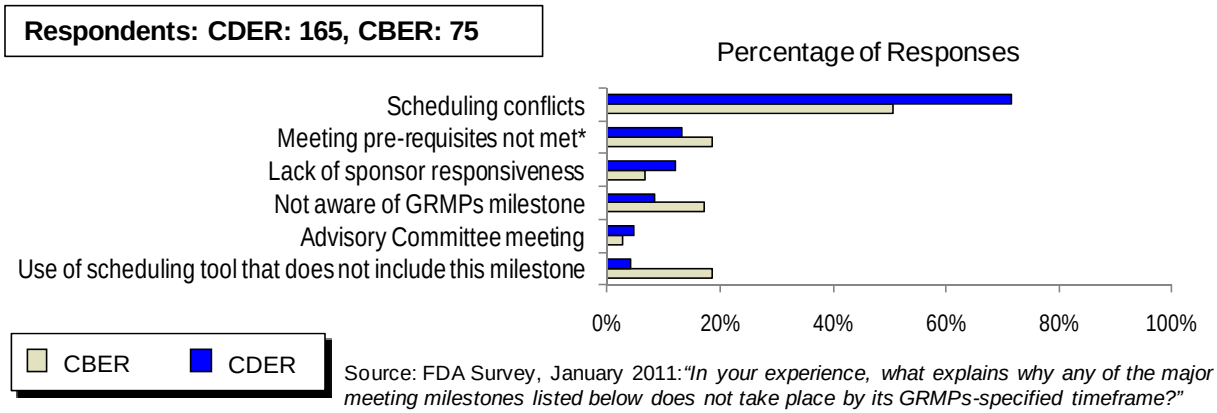
There was an organizational expectation in CDER and CBER that all key disciplines attend the major review meetings. Nearly all RPMs interviewed agreed that review team staff take major review meetings seriously and will designate their team leader or appoint another representative to attend in their place if the primary reviewer cannot attend. A few RPMs, who regularly invite all discipline reviewers, reported challenges obtaining consistent attendance from certain reviewers (e.g., labeling, compliance, reviewers from other Centers in cases of combination product reviews). During interviews, some RPMs described inconsistent attendance to be due to a low prioritization of meetings by these reviewers when invited (OSE, OC), and attendance of different representatives of a review division/office. These issues have led to gaps in communication and the need for RPMs to follow up more frequently with disciplines. Other potential reasons for inconsistent attendance are that OSE and OC reviewers reported that they were not always informed of or aware that meetings were taking place, or could not attend due to workload conflicts.[69]

Currently, the most common practice used by RPMs is to schedule most major meetings during the first two weeks when the review team is assigned and assembled. The filing/planning meeting and mid-cycle meeting are most typically scheduled at the same time, while the wrap-up meeting is often scheduled after the mid-cycle meeting has been completed and the need for

[69] These reasons were cited based on FDA survey responses, January 2011. See Exhibit 25 and Exhibit 30 for OSE and OC responses regarding meeting attendance.

an Advisory Committee has been determined. Despite the RPMs' general practice of scheduling meetings early in the review according to the GRMPs milestone dates, scheduling conflicts are prevalent across all major meetings and were the most typically cited source of meeting delays and rescheduled dates. Exhibit 17 illustrates the large percentage of FDA staff (72%, 119 of 165, CDER, 51%, 38 of 75, CBER) that reported scheduling conflicts as the primary factor impacting adherence to the *Hold Filing Meeting* milestone. These results were consistent with those for the *Mid-Cycle Meeting* and *Wrap-up Meeting.* Scheduling conflicts arose from challenges in coordinating calendars for a large number of meeting participants (ranging from 10 to 40), difficulties scheduling around leadership staff calendars, and navigating discipline reviewers' competing commitments from other application submissions and deadlines.

**Exhibit 17. Factors Impacting Non-adherence to *Hold Filing Meeting* Milestone by Center**




Source: FDA Survey, January 2011:*"In your experience, what explains why any of the major meeting milestones listed below does not take place by its GRMPs-specified timeframe?"*
* Meeting pre-requisites include meeting deliverables incomplete, last minute revisions being made with review

In addition to scheduling conflicts, late mid-cycle meetings were frequently attributed to incomplete deliverables[70] or last minute revisions on presentation materials, while late wrap-up meetings were attributed by FDA respondents to AC meetings and to applicant unresponsiveness. A notable difference between CDER and CBER is that a consistently higher proportion of staff in CBER indicated that their scheduling tools did not track milestones for the major meetings.[71]

### 4.2.3. Request Consults

Consult requests met the GRMPs-specified timelines in only 16% (10/61) of cohort applications, the lowest adherence level among all planning phase milestones. Most application reviews require more than one consult; in the application cohort, application reviews required an average of three consult requests (ranging from one to seven). To be considered adhering to GRMPs timeframes, all consults required for an application review must be completed by day 45/30 (standard/priority).

[70] Interim deliverables are discipline planning tools used by CDER as part of the 21st Century Review to allow review team members to establish overall schedules for their reviews. Mid-Cycle meetings are used to discuss preliminary findings, interim deliverables, and any problems reviewers have identified. Incomplete deliverables were frequently mentioned by RPMs as a factor in delaying the date of Mid-Cycle meetings.
[71] FDA Survey, January 2011. The response "Use of scheduling tool does not include this milestone" was more frequently selected by CBER respondents than by CDER respondents for the major meetings, including *Hold Filing Meeting* (19% CBER, 4% CDER), *Mid-Cycle Meeting* (10% CBER, 4% CDER), and *Wrap-up Meeting* (12% CBER, 2% CDER).

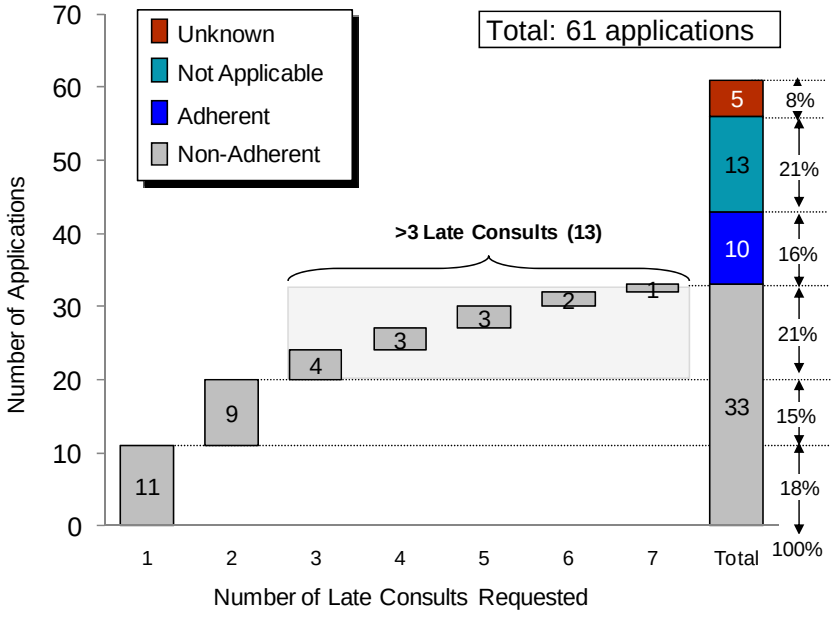
Consults tended to be requested in a larger number of cohort applications reviewed by CDER than for CBER (Exhibit 18). Of the 12 CBER applications in the study cohort, 3 applications requested consults (25%), whereas all aspects of the review were performed by members of the CBER review team for the remaining applications. In comparison, 86% (42/49) of CDER cohort applications requested consults.

**Exhibit 18. Consult Requests by Center, CDER and CBER**

| Center | Number of Applications with Consult Requests | GRMPs-Adherent Consult Requests |
|---|---|---|
| **CDER** | 86% (42/49) | 21% (9/42) |
| **CBER** | 25% (3/12) | 33% (1/3) |

Exhibit 19 summarizes adherence of consult requests to GRMPs-specified timeframes and the number of applications that had one or more late consults. Trade name/patient package insert (PPI), pregnancy labeling, risk, and environmental assessment (EA) consults were considered "frequently occurring" consults according to GRMPs guidance,[72] but constituted 57% of applications with one late consult. Among the 35 applications that did not meet GRMPs-specified timeframes for completion of consult requests, the majority experienced more than one late consult request; 26% of these applications were associated with two consult requests initiated late, while 37% were associated with three or more late consult requests.

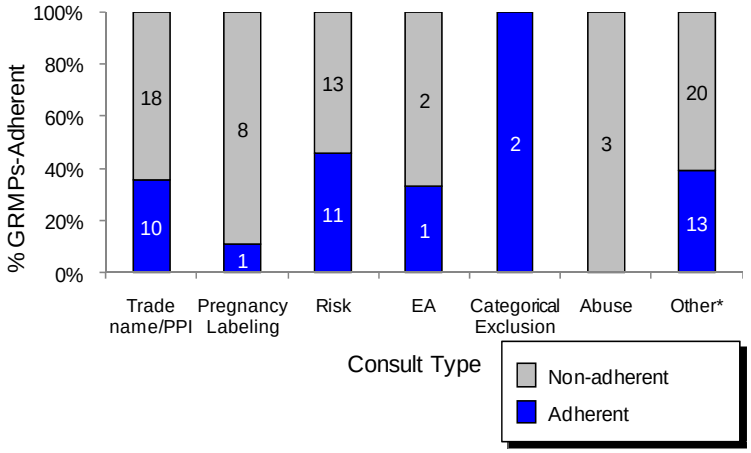
**Exhibit 19. GRMPs Adherence with Requesting Consults**




[72] According to GRMPs Guidance, six "frequently occurring" consults were listed to include: Trade name/PPI, pregnancy labeling, risk, environmental assessments (EA), abuse potential, and categorical exclusions.

Interviews with RPMs and focus groups with discipline reviewers indicated uncertainty among the review team as to which consult requests are considered standard. More than half of each type of "frequently occurring" consult was initiated after the specified 45/30 day timeframe (Exhibit 20), except for categorical exclusion requests, which were consistently issued on or before the indicated timeframe.

**Exhibit 20. Adherence of Frequently Occurring Consult Types to GRMPs-Specified Timeframes**

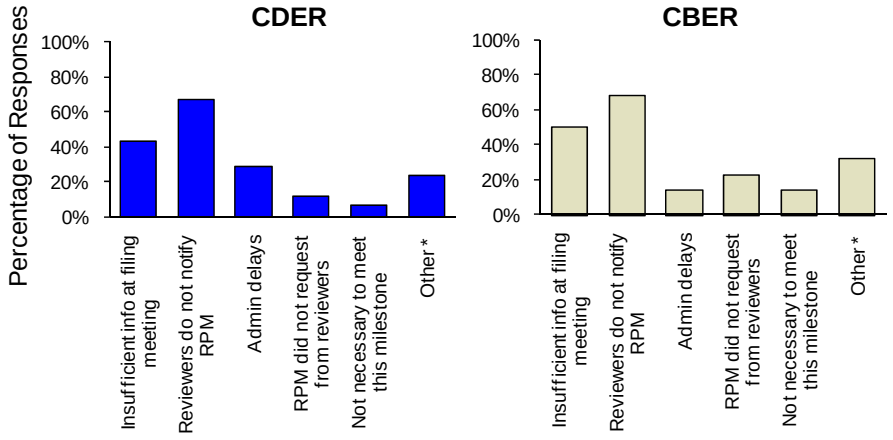



Notes: Number of consults by type are based on a count of all consults requested in our application cohort; due to the variation in the number of consults and the consult types requested for each application, there is no consistent total for any particular consult type; there were no late consults for categorical exclusions

* "Other" consult types include: Pediatric, Immunogenicity, IRT/QT, CDRH, NHLBI, and discipline consults (e.g., dermatology, cardio-renal, microbiology, ophthalmology)

RPMs attributed late consult requests to challenges in predicting which consults were necessary in the first 45/30 days of review and the failure of reviewers to notify the RPM of needed consults prior to the filing meeting (67%, 30/45 in CDER; and 68%, 15/22, in CBER), as the need is often identified by discipline reviewers during the review phase, after the filing meeting occurs. As shown in Exhibit 21, FDA staff also noted that at the time of the filing meeting, there is often insufficient information to determine the need for a consult (47%, 21/45 in CDER; and 50%, 11/22, in CBER).

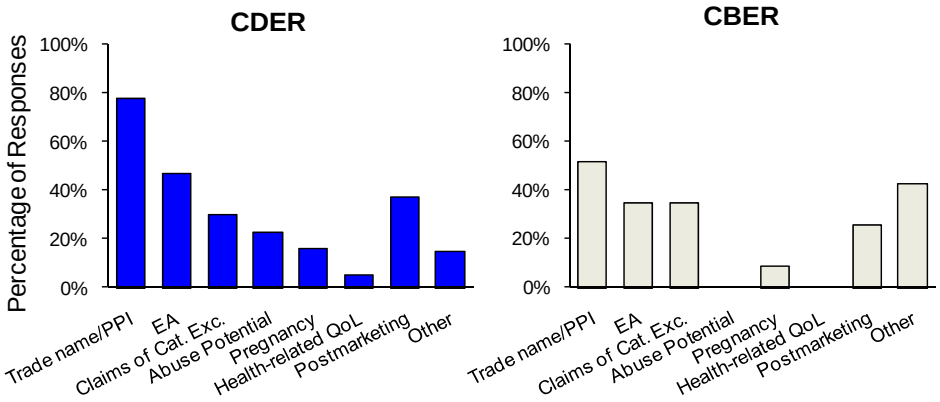
**Exhibit 21. Common Reasons for Late Consult Requests**




Source: FDA Survey, January 2011:*"What are the typical reasons why standard consults are requested late?"*
* Other responses often reiterated selections made by respondents and did not reflect any specific category or issue

When asked which consult requests were most predictable, more than half of CBER RPMs (52%) and the majority of CDER RPMs (78%) surveyed agreed that consults for labeling/PPI, which include consults to SEALD, OMP, OSE, and DDMAC, were most predictable (Exhibit 22).

**Exhibit 22. Consult Types Considered "Standard" by Center**

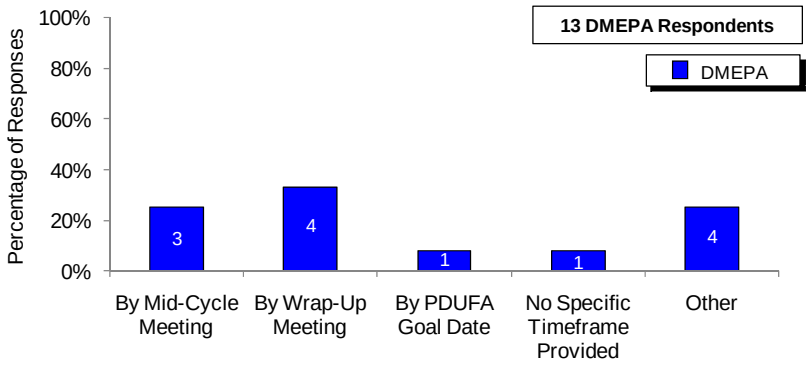



Source: FDA Survey, January 2011:*"What consults do you consider standard?"*

OSE representatives are typically requested by review teams to complete labeling reviews by the mid-cycle or wrap-up meetings, as shown in Exhibit 23. However, despite the fact that labeling consults were determined to be most predictable, DMEPA and DRISK staff commented that one of the primary reasons they experienced challenges with completing labeling reviews within requested timeframes was that they were not consulted until late in the review process, leaving insufficient time to conduct reviews.[73]

[73] FDA OSE Survey, January 2011. Of the 12 OSE staff who responded to the question: "*In your experience, what are the main challenges in completing the labeling review within GRMPs timeframes?",* 7/12 respondents reported competing workload as a key factor, and 5/12 respondents reported that they are not usually consulted until late in the review process.

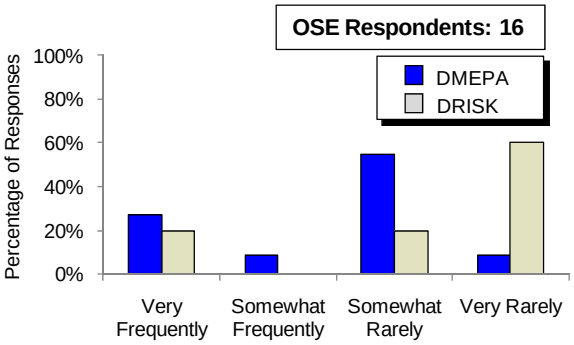
**Exhibit 23. Requested Completion Times for Labeling Reviews by Review Teams**




Source: FDA OSE Survey, January 2011:*"When are you typically asked to complete the labeling review?"*

One contributing factor to late notification of OSE staff to conduct labeling reviews is that these reviewers infrequently attend filing meetings. According to the OSE survey, 80% of DRISK respondents and 64% of DMEPA respondents reported rarely attending the filing meeting (Exhibit 24).

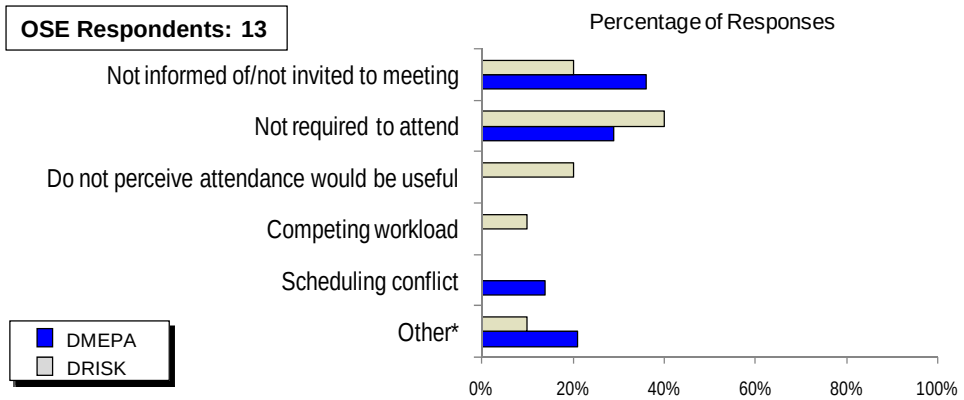
**Exhibit 24. OSE Attendance at Filing Meeting**




Source: FDA OSE Survey, January 2011:*"How frequently do you attend each of the major meetings?"*

The two most frequently mentioned reasons for infrequent attendance were that OSE staff were not informed of or not invited to attend the filing meeting, and that they did not perceive that their attendance was required (Exhibit 25).

**Exhibit 25. Common Reasons for Infrequent Filing Meeting Attendance**




Source: FDA OSE Survey, January 2011:*"If you answered 'Somewhat rarely' or 'Very Rarely', what are the most common reasons for not attending more regularly?"*

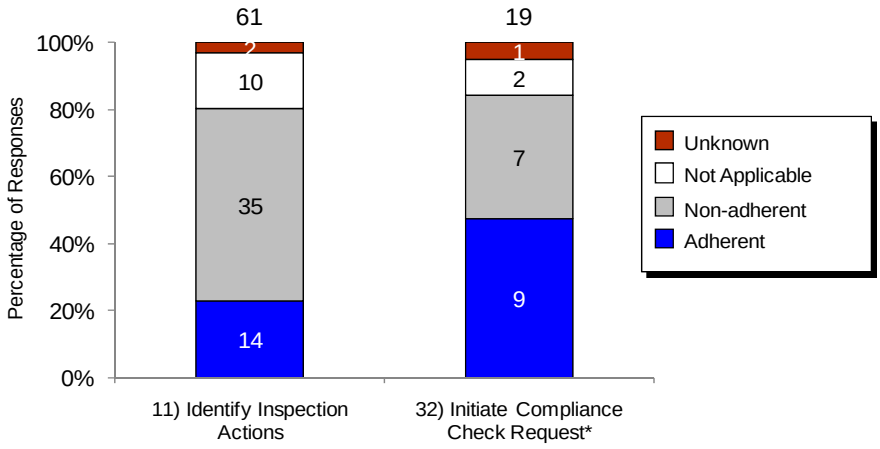
Although a few RPMs mentioned that inspection actions are occasionally identified as early as the pre-NDA/BLA meeting, RPMs were not in agreement that any of the other "frequently occurring" consults in Exhibit 22 could be anticipated early in the review cycle, and often waited until discipline reviewers discuss them during meetings to initiate the consults.

### 4.2.4. Request Inspection Actions and Issuing Compliance Check Requests

Another request identified during the planning phase, *Identifying Inspection Actions*, was often performed after GRMPs timelines, with adherence of only 29% (14/49) for identifying inspection actions within 45 days of application receipt for Standard reviews and 30 days for Priority reviews (Exhibit 26). Inspection action requests include submitting Establishment Evaluation Requests (EER) and requesting inspections for NDAs, coordinating pre-approval inspections (PAIs) for BLAs, and requesting investigations of clinical, non-clinical, and biopharmaceutics research sites.[74] Late identification of inspection actions differs by Center and by application review type, with an average of 86 days late for CBER BLAs, 69 days late for CDER BLAs, and 20 days late for CDER NDAs.

[74] Per GRMPs Guidance, EER is submitted by ONDC or OBP (CDER) and DMPQ (CBER); PAIs are submitted by DMPQ or product reviewers (CDER or CBER); requests for investigation of clinical, non-clinical, and biopharmaceutics research sites are initiated by DSI (CDER) or BiMo (CBER). Dates for clinical and manufacturing inspection requests are used by the analysis team when available in FDA electronic systems for cohort applications; however, manufacturing inspection requests are typically recorded in a separate FDA data system (Establishment Evaluation System) and unavailable for analysis.

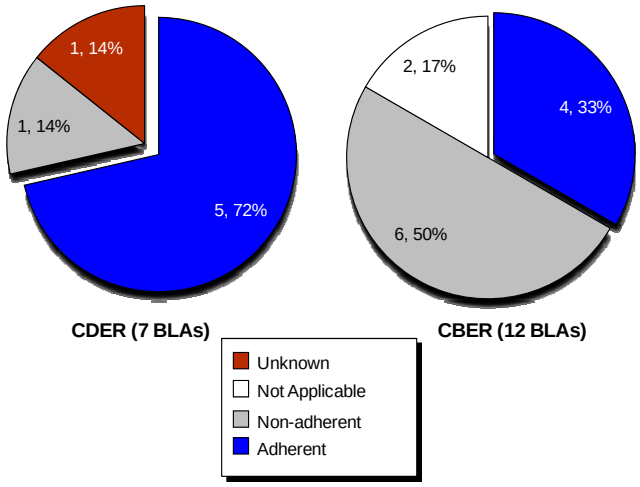
**Exhibit 26. GRMPs Adherence for Identifying Inspection Actions and Issuing Compliance Check Requests**




* This step, *Compliant Check Request,* only pertains to BLAs (19); NDAs are not included.

Another internal request, *Initiate Compliance Check Request*, is issued during the action phase four weeks prior to approval. Compliance check requests are conducted only for BLAs to determine whether the establishment and product meet proper manufacturing controls to ensure product safety, purity, and potency, including good manufacturing practices regulations (GMPs).[75] Based on available data points (16/19 applications), more than half of compliance checks were initiated on time (56%) (Exhibit 27). However, adherence on this step differed by Center, and was higher for CDER BLAs (72%, 5/7) than CBER BLAs (33%, 4/12).

**Exhibit 27. GRMPs Adherence for Issuing Compliance Check Requests by Center**

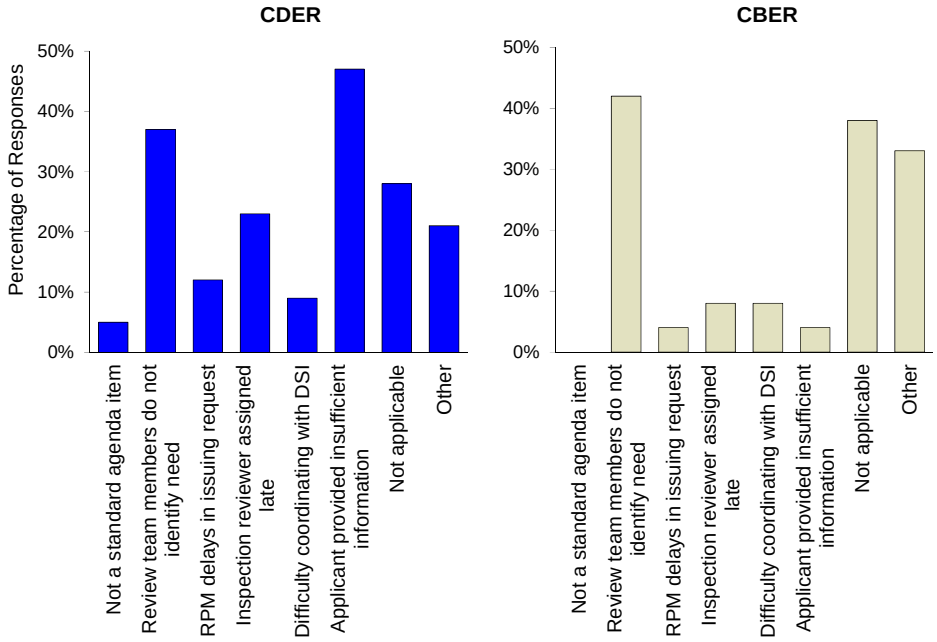



Interviews with RPMs indicated that reviewers (e.g., DSI, BiMO, medical officers, DMPQ) commonly identified the need for inspection actions during or after the time of the filing meeting.

[75] Biologics Procedures SOPP 8407, Version #4: Compliance Check Requests, "The compliance status of the manufacturer's applicable product(s) and establishments(s) shall be determined prior to rendering a final decision regarding applications and application supplements."

Often the need for inspections and the number of potential sites to be inspected were communicated electronically before the filing meeting or were discussed during the filing meeting. However, RPMs also report that for application reviews that did not adhere to GRMPs timeframes, the need for inspection actions was not identified until later in the review cycle (e.g., mid-cycle review) by members of the CDER and CBER discipline review team (Exhibit 28). While CDER RPMs most frequently indicated that insufficient information provided by applicants was a factor behind late identification of inspection requests (47%), CBER staff rarely indicated that insufficient information was a factor (4%).

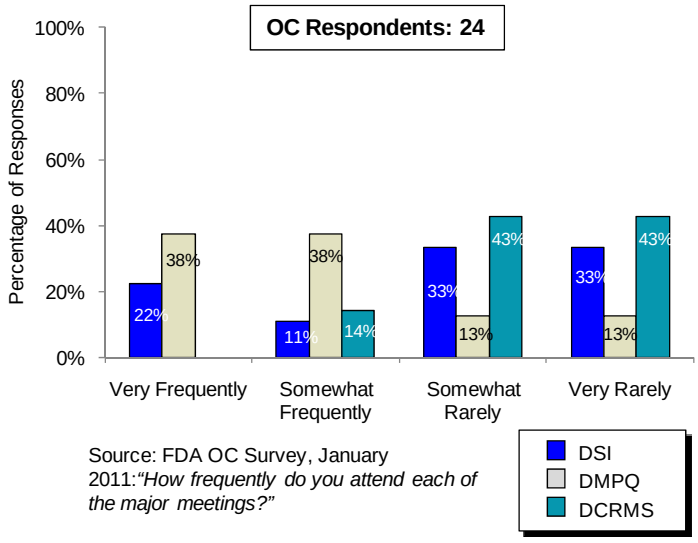
**Exhibit 28. Factors Driving Late Identification of Inspection Requests**




Source: FDA Survey, January 2011:*"What are the most common reasons for late inspection requests?"*

Findings from the FDA survey issued to CDER Office of Compliance (OC) staff suggests that infrequent attendance of OC staff at the filing meeting is another cause of late identification of inspection actions. DSI inspections need to be identified early in the review process; however, the majority of DSI staff (67%, 6/9) rarely attended the filing meeting when the need for inspection actions could be discussed (Exhibit 29).

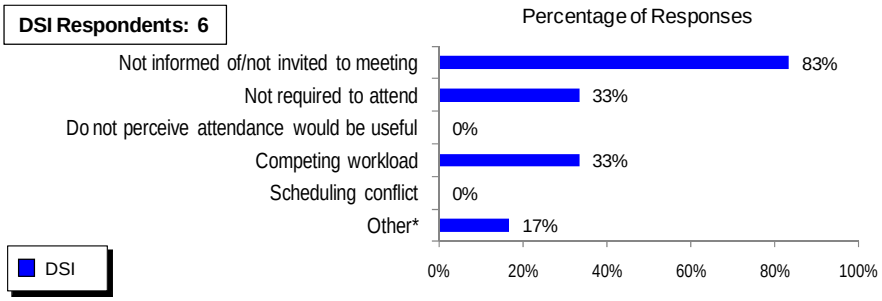
**Exhibit 29. CDER OC Attendance at Filing Meeting**




Source: FDA OC Survey, January 2011:*"How frequently do you attend each of the major meetings?"*

DSI representatives most frequently report that the primary reason why they rarely attend filing meetings is due to the fact that they were not informed of or invited to attend the meeting (83%, 5/6) (Exhibit 30). A lack of perceived requirement to attend the meeting as well as competing workload were also cited as factors impacting infrequent filing meeting attendance.

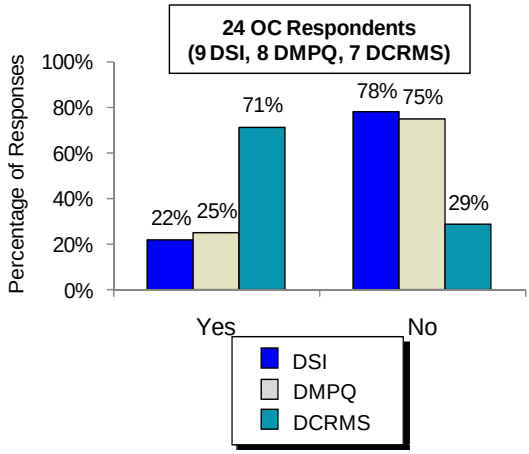
**Exhibit 30. Common Reasons for Infrequent Filing Meeting Attendance**




Source: FDA OC Survey, January 2011: *"If you answered 'Somewhat rarely' or 'Very Rarely', what are the most common reasons for not attending more regularly?"*

RPMs reported that once inspection actions were identified, there were no firm timelines for the inspection completion, which could contribute to overall delays in the review process. The majority of Division of Scientific Investigation (DSI) staff (78%, 7/9) and Division of Manufacturing and Product Quality (DMPQ) staff (75%, 6/8) who participated in the FDA OC survey indicated that there was insufficient time in the review process to complete inspection actions (Exhibit 31). By contrast, 29% (2/7) of respondents from the Division of Compliance, Risk Management and Surveillance (DCRMS) reported insufficient time to complete inspections actions. However, DCRMS usually has a more limited role and is involved in later stages of the application review process than DSI (e.g., evaluation of REMS).

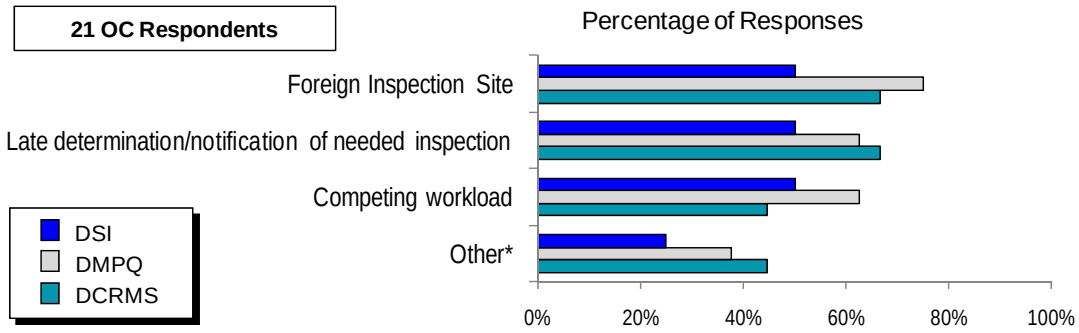
**Exhibit 31. FDA Office of Compliance Responses on Whether There is Sufficient Time to Conduct and Coordinate Inspections**




Source: FDA OC Survey, January 2011:*"Is there sufficient time in the current process to conduct/coordinate inspections?"*

CDER Office of Compliance staff was also asked to provide feedback on the causes for delays in completing inspection actions (Exhibit 32). Delays in completing inspections were most frequently attributed to the need to inspect foreign facilities, followed by late determination of needed inspections, and competing workload. The late notification of needed inspections is consistent with the reason provided by DSI and shown in Exhibit 30 that DSI staff are often uninformed or not invited to attend the filing meeting, when the need for inspections are often initiated and discussed. OC staff also commented that it is much more challenging to coordinate inspections for priority versus standard reviews, and that priority reviews with foreign establishments are especially difficult to coordinate within the review timeframe.

**Exhibit 32. Factors Driving Insufficient Time for Inspection Coordination and Completion**




Source: FDA OC Survey, January 2011:*"When there is not sufficient time to coordinate/complete inspections, what are the most common reasons?"*
* Other comments include difficulties coordinating inspections for priority reviews and/or priority supplements

## 4.3. Detailed Findings for Selected Review and Advisory Committee Phase Milestones

The following GRMPs steps pertaining to the Review and Advisory Committee Phase are discussed in this section:

- *Complete Primary Review* (Step 20) – This section provides a general overview of the overall cohort as well as a more detailed analysis including a comparison of adherence by discipline review type and factors that impact adherence to this GRMPs step.

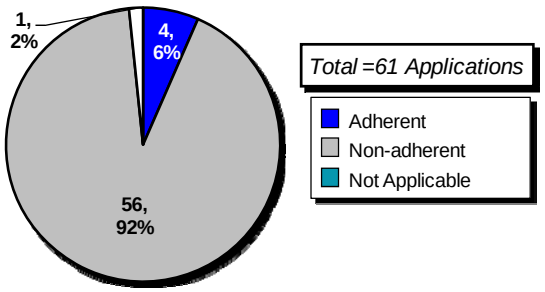
- AC Meeting steps, which include:
  - *Plan AC Meeting* (Step 24)
  - *Disseminate and disclose applicant and FDA background materials* (Step 25)
  - *Conduct AC Meeting* (Step 26)
  - *Internal meetings to integrate AC input* (Step 27)
  - *Confidential memo to AC to announce action* (Step 28)

### 4.3.1. Complete Primary Reviews

Of the ten GRMPs milestones in the review phase, *Complete Primary Review* is the most significant and complex step in the course of the review, requiring the coordination and completion of application review among all discipline reviewers. The GRMPs specify that primary reviews must be completed by the end of month 8/5 (Standard/Priority). Application reviews considered non-adherent to GRMPs milestones were those with one or more disciplines that had logged completed reviews with secondary signatures into FDA IT systems after the specified timeframes. Detailed criteria used to assess adherence to GRMPs for this step is also summarized in Exhibit 7.

The highest level of overall GRMPs non-adherence occurred with this step. Analysis of electronic and hard copy action packages indicated that primary discipline reviews were completed on time for only 6% (4/61) of cohort applications (Exhibit 33). Since 92% (56/61) of cohort applications completed reviews after the GRMPs-specified timelines, non-adherence appears to be unrelated to adherence with previous milestones or specific application characteristics (e.g., CDER vs. CBER, priority vs. standard, NME vs. non-NME).

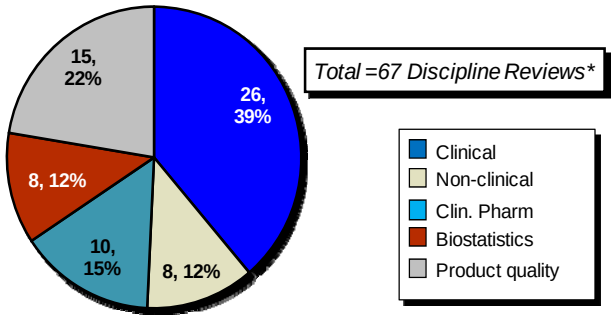
**Exhibit 33. GRMPs Adherence for Completing Primary Reviews**




Among the review disciplines, the clinical discipline was most frequently the last to complete its review (39%, 26/67), while biostatistics and non-clinical disciplines were least often the last to complete reviews (Exhibit 34). Clinical reviewers typically require input from other discipline

reviews, such as biostatistics, product quality, and clinical pharmacology, in order to complete the primary clinical review. Interdependencies also exist in other disciplines, so clinical pharmacology reviewers also rely on data from the clinical, product quality, and non-clinical reviews to complete their primary reviews.

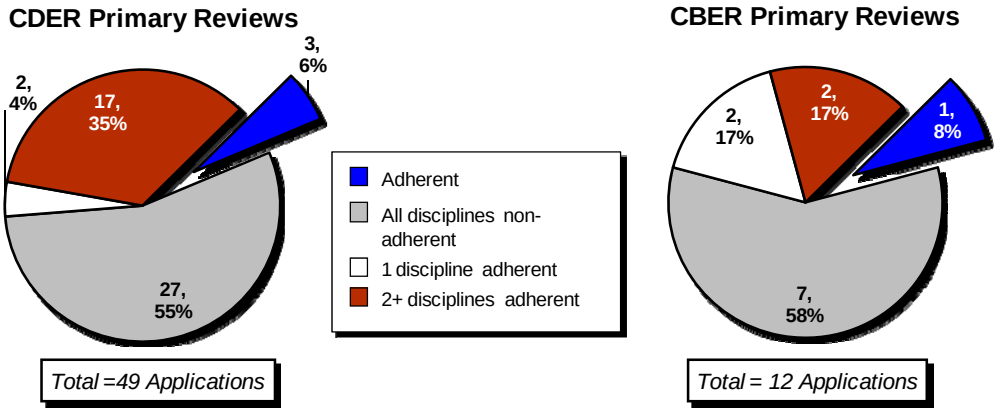
**Exhibit 34. Last Review Discipline to Complete Primary Review**




* Note: For seven applications, two review disciplines were simultaneously last to complete review, resulting in 67 total review disciplines for 61 applications (1 withdrawn)
Sources: DARRTS, RMS/BLA – Final Review memo dates per discipline logged into IT system

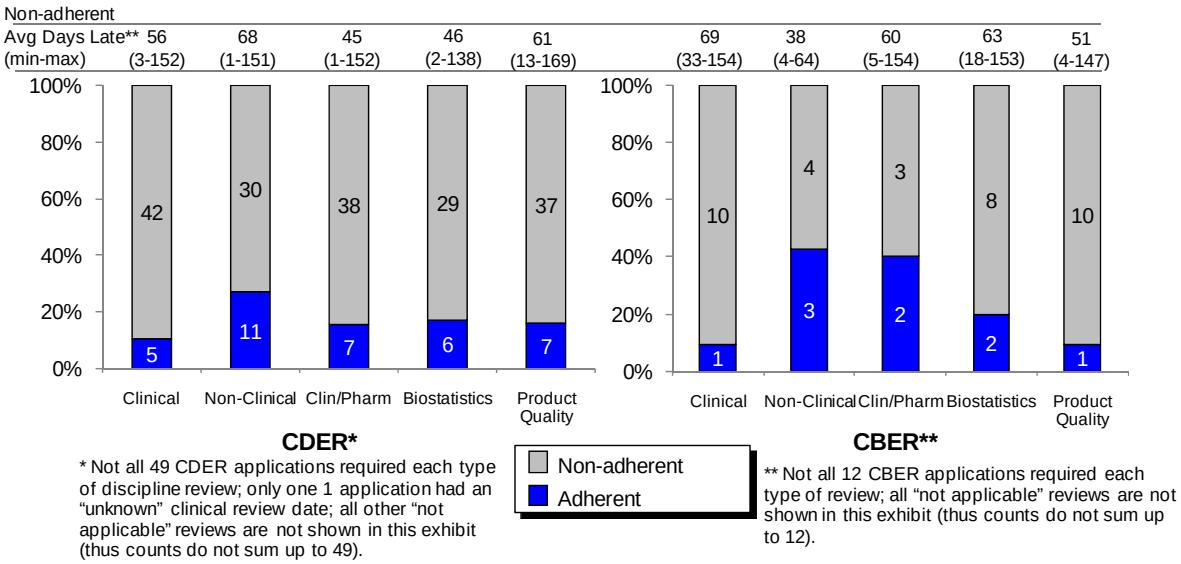
Nearly all CDER and CBER primary reviews were completed after GRMPs timelines (Exhibit 35). Among CDER NDAs, 94% (46/49) of applications did not meet GRMPs adherence for completing primary reviews. Similarly, 92% (11/12) of CBER BLAs did not meet GRMPs adherence for completing primary reviews.

**Exhibit 35. GRMPs Adherence for Completing Primary Reviews by Center**




The vast majority of non-adherent applications involved more than one late review discipline (96% in CDER, 82% in CBER). The most frequently late review disciplines included clinical, clinical pharmacology, and product quality reviews in CDER, and clinical and product quality reviews in CBER. Reviews that did not adhere to the GRMPs milestone averaged 45-68 days late in CDER, and 38-69 days late in CBER (Exhibit 36). For application reviews that did not adhere to the GRMPs milestone, detailed distribution curves in Appendix F display the number of days late by which reviews were completed for each primary review discipline.

**Exhibit 36. GRMPs Adherence for Completing Primary Reviews by Discipline Review Type for CDER and CBER (Based on total number of applications)**




* Not all 49 CDER applications required each type of discipline review; only one 1 application had an "unknown" clinical review date; all other "not applicable" reviews are not shown in this exhibit (thus counts do not sum up to 49).

** Not all 12 CBER applications required each type of review; all "not applicable" reviews are not shown in this exhibit (thus counts do not sum up to 12).

** Detailed distribution curves display the number of days late in completing primary reviews for each discipline and are available in Appendix F.

While the majority of cohort applications did not adhere to this GRMPs milestone, four cohort applications completed all discipline primary reviews on time.

Three of the four applications that were compliant with completing primary reviews were approved BLAs. In addition, three applications had Priority review designation, including two reviewed under accelerated approval. Two applications included major amendments, both of which were submitted approximately one month prior to the original primary review date milestone, which extended the time available to complete all discipline reviews by three months. All four applications required or requested a PMR or PMC.

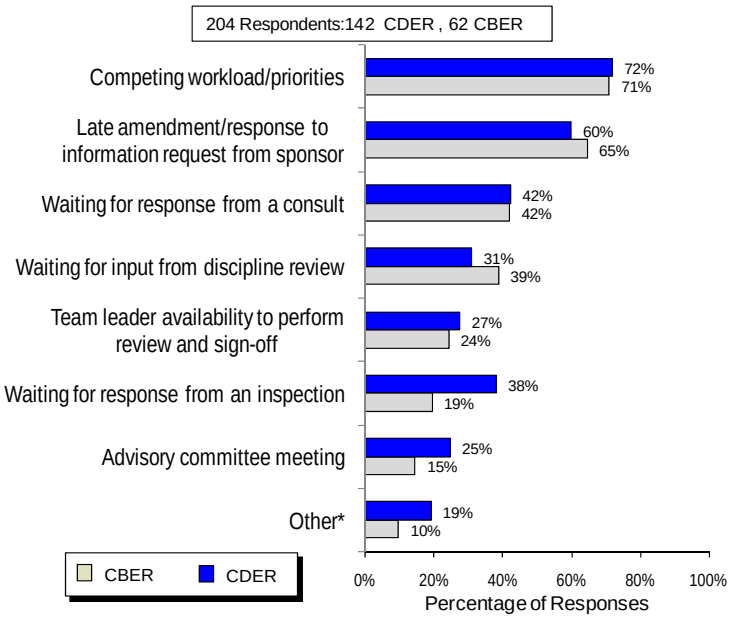
These applications do not appear to differ significantly from other cohort applications in the study in terms of GRMPs adherence of preceding milestones (steps 1-19). A summary of selected application characteristics for the four compliant applications is included in Exhibit 37.

**Exhibit 37. Selected Characteristics of Applications Adherent with Completion of Primary Review**

| NDA/ BLA | Center | Division | Original/ Supplement | Priority/ Standard | Accelerated Approval | Major Amendment | AC Meeting | REMS | PMR/ PMC | FDAAA PMR | Adherent Mid-Cycle Meeting | Action |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BLA | CDER | DBOP | Original | Priority | Yes | Yes | Yes | Yes | Yes | Yes | Unknown | Approved |
| BLA | CDER | DBOP | Supplement | Priority | No | Yes | No | No | Yes | Yes | No | Complete Response |
| NDA | CDER | DNCE | Original | Standard | No | No | No | No | Yes | No | Yes | Approved |
| BLA | CBER | OVRR | Original | Priority | Yes | No | No | No | Yes | No | Yes | Approved |

The low adherence of the *Complete Primary Review* milestone step was most frequently attributed to a few key drivers in RPM interviews and discipline focus groups. Findings from the FDA survey indicate that competing workload was most frequently cited as a factor for low adherence (72%, 102/142 in CDER, and 71%, 44/62 in CBER), followed by late amendments from applicants, and internal delays from other review disciplines and consults (Exhibit 38).

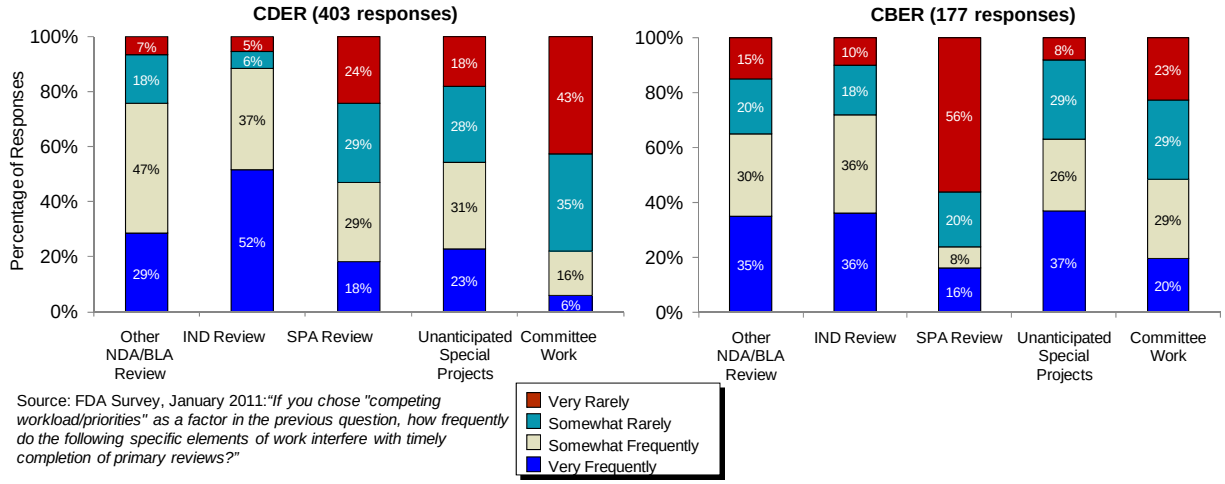
**Exhibit 38. Factors Impacting GRMPs Adherence for Completion of Primary Reviews**




Source: FDA Survey, January 2011:*"In your experience, what factors are the most common barriers to completing the primary review on time? Please mark all that apply."*

When probed further on which aspects of workload were most disruptive to an application review, RPMs and discipline reviewers commented that their time and effort is regularly spread to concurrently perform other NDA reviews, IND reviews, unanticipated projects, and committee work (Exhibit 39). Of these, IND reviews performed concurrently with an NDA/BLA appeared to be the most frequently disruptive factor (89%, 85/96 in CDER, 72%, 28/39 in CBER), followed by other NDA/BLA reviews (76%, 70/92 in CDER, 65%, 26/40 in CBER). The short timeframe permitted for an IND review often required reviewers to place a higher priority on the IND review completion, instead of completing the primary review for standard or priority NDA/BLA. Team leaders and supervisors delegated work to reviewers by examining review calendars and considering individual workload. Reviewers generally described work assignments as being fair and balanced in light of resource limitations. Other types of competing workload commented on by staff include: industry meetings (Type B, Type C, pre-IND/IDE), training sessions, guidance development, supplement reviews, and participation in biomarker qualification review teams.

**Exhibit 39. Types of Competing Workload Reported to Interfere with Timely Completion of Primary Reviews**




Source: FDA Survey, January 2011:*"If you chose "competing workload/priorities" as a factor in the previous question, how frequently do the following specific elements of work interfere with timely completion of primary reviews?"*

Another frequently-cited cause of non-adherence to timely completion of primary reviews was failure among multiple review disciplines to coordinate review completion in an efficient and timely manner. Each NDA/BLA review typically required coordinated completion by two or more disciplines. While these disciplines were highly interdependent, no internal timelines or sequence of completion was in place. This lack of systematic processes, combined with infrequent or poor communication between review disciplines, contributed to review inefficiencies. For example, due to the types of information needed in a clinical review, a clinical discipline reviewer must often wait for all other review disciplines to complete their reviews before completing the clinical review.

Exhibit 40 summarizes FDA survey findings from CDER and CBER discipline reviewers who were asked to indicate which discipline reviews they were dependent upon to complete their own reviews. Clinical reviewers in both Centers most frequently indicated a dependency on inputs from all other review disciplines, while clinical pharmacology, biostatistics, and product quality reviewers less frequently indicated a dependency on other disciplines to complete their review. Findings were similar across Centers with few exceptions. For example, CBER clinical reviews less frequently relied on clinical pharmacology and product quality reviews than in CDER. Moreover, CBER non-clinical reviews were more frequently dependent on biostatistics reviews than in CDER.

**Exhibit 40. Primary Review Dependencies Reported by Discipline Reviewer Type**

**A. CDER Survey Responses**

| | Primary Review Dependencies | | | | | |
|---|---|---|---|---|---|---|
| **CDER Discipline Reviewer Type** | Clinical | Non-Clinical | Clinical/ Pharmacology | Product Quality | Biostatistics | No Dependencies |
| Clinical (58) | 14% | 52% | 67% | 45% | 78% | 12% |
| Non-Clinical (28) | 18% | 4% | 14% | 43% | 11% | 46% |
| Clinical/ Pharmacology (12) | 42% | 8% | 0% | 8% | 0% | 58% |
| Product Quality* (29) | 3% | 34% | 14% | 17% | 10% | 59% |
| Biostatistics (11) | 82% | 0% | 0% | 0% | 0% | 18% |

**B. CBER Survey Responses**

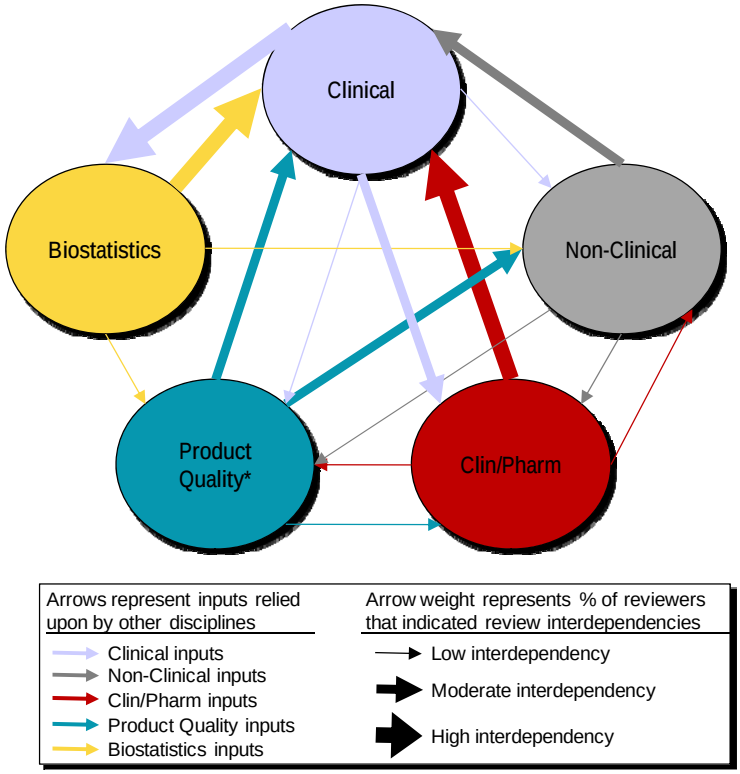
| | Primary Review Dependencies | | | | | |
|---|---|---|---|---|---|---|
| **CBER Discipline Reviewer Type**** | Clinical | Non-Clinical | Clinical/ Pharmacology | Product Quality | Biostatistics | No Dependencies |
| Clinical (8) | 38% | 63% | 13% | 13% | 75% | 13% |
| Non-Clinical (10) | 20% | 60% | 10% | 30% | 50% | 0% |
| Product Quality* (34) | 9% | 15% | 6% | 44% | 15% | 44% |
| Biostatistics (6) | 67% | 0% | 0% | 0% | 0% | 33% |

Source: FDA Survey, January 2011. *"On which discipline reviews are you typically dependent to complete your review?"*.
* Product Quality includes Chemistry, Manufacturing, and Control (CMC) reviews and GXP/Facility reviews.
** No Clinical/Pharmacology reviewers responded to this survey question, so no data are available for CBER regarding Clin/Pharm dependencies.

The level of interdependencies derived from FDA survey data were also mapped in the network diagram shown in Exhibit 41, which illustrates the complex relationships between primary review disciplines, and underscores the need for all disciplines to coordinate early and often to promote timely completion of all primary reviews.[76] All disciplines receive critical inputs from at least one other review discipline, but clinical reviews were most heavily dependent on the seamless coordination and completion of reviews from all other disciplines in order to complete their reviews. Late completion of any of these discipline reviews impinged on timely completion of clinical reviews, which supports earlier findings from the GRMPs assessment that clinical reviews are often the last discipline to complete primary reviews.

[76] For the purposes of this illustration, Product Quality combines Chemistry, Manufacturing and Control (CMC) reviews and GXP/Facility Reviews. However, there are notable functional differences between the two roles. CMC reviewers participate in reviewing sections of product application submissions and exchange these reviews with other disciplines, while GXP/Facility representatives coordinate the inspection of applicant GXPs in the field, review and report on inspection findings, and exchange findings with CMC and Clinical reviewers. Each of the two functional roles is subject to experiencing delays due to interdependencies with other disciplines.

**Exhibit 41. Network Diagram of Discipline Review Interdependencies**




Source: FDA Survey, January 2011. *"On which discipline reviews are you typically dependent to complete your review?"*.
* Product Quality includes Chemistry, Manufacturing, and Control (CMC) reviews and GXP/Facilities

In addition to dependencies among key disciplines (clinical, non-clinical, clin/pharm, biostatistics, product quality), reviewers also frequently cite late completion of labeling reviews and inspection reviews as contributing to the late completion of primary reviews. As described in a previous section of this report, neither labeling reviews nor inspection reviews are currently held to an individual GRMPs milestone and late notification of the need for labeling and inspection reviews also contribute to the finding that these reviews are often not completed until or just prior to the PDUFA goal date. Some review team members had a different understanding and definition of what constitutes a completed primary review. Feedback from RPMs and discipline review focus groups indicated a primary review is complete only after it has received secondary sign-off and has been logged into FDA systems. This is consistent with the CDER definition for completion of primary review, per the 21st Century Review Desk Reference Guide.[77] While the majority of CDER review team staff (73%, 159/218) and CBER review team staff (55% 46/84) agreed with this definition, some review team members considered a primary review to be complete as long as a discipline review had been drafted, even if the review still awaited secondary sign-off. RPMs mentioned this factor as a potential cause of delays (Exhibit

[77] According to the CDER 21st Century Review Process Desk Reference Guide (version dated 1/4/2011): "A primary review is considered final only after it has been reviewed, signed-off by the discipline team leader, and archived. The TL should type "I concur" when signing off in FDA electronic systems if there is concurrence between TL and reviewer and no additional TL review will be completed. The sign-off indicates the review is complete and the team leader has read it."

42). Focus groups also indicated that few reviewers log reviews into the IT system until secondary sign-off is completed.

The cause of such variability in interpretation of this milestone is likely due to differences in the usage of FDA IT systems by CDER and CBER. FDA survey findings indicate that the practice of reviewers logging completed reviews into the system is limited to CDER. Over one-third of CBER respondents to the FDA survey defined a completed primary review as one that was drafted but not yet entered into FDA systems. This is explained by review staff feedback that the FDA data system used by CBER is not generally used as a repository for discipline reviewers to actively share reviews, and that log-in ability is usually limited to RPMs rather than review staff in CBER. The variability in definitions of this milestone between Centers suggests that late completion of primary review as assessed using FDA data systems may not correspond to whether a substantive review is actually completed.

**Exhibit 42. FDA Staff Definition of *Complete Primary Review***

| Definition Type | CDER (215 responses) | CBER (84 responses) |
|---|---|---|
| The review is drafted by a discipline reviewer, received secondary sign-off, and logged into DARRTS or RMS/BLA | 73% (157 responses) | 55% (46 responses) |
| The review is drafted by a discipline reviewer and received secondary sign-off, but not yet logged into DARRTS or RMS/BLA | 12% (26) | 33% (28) |
| The review is drafted by a discipline reviewer, awaiting secondary sign-off and not yet logged into DARRTS or RMS/BLA | 7% (14) | 7% (6) |
| Other* | 8% (18) | 5% (4) |

Source: FDA Survey, January 2011:*"In your opinion, a primary review is considered complete when…"*

** A few CBER respondents (3) commented that RMS/BLA is not frequently used as a review repository, and thus CBER review staff do not consider logging a review into RMS/BLA as a necessary step in defining completion; a few CDER respondents (3) commented that a review could be considered complete if logged into DARRTS without a secondary signature*

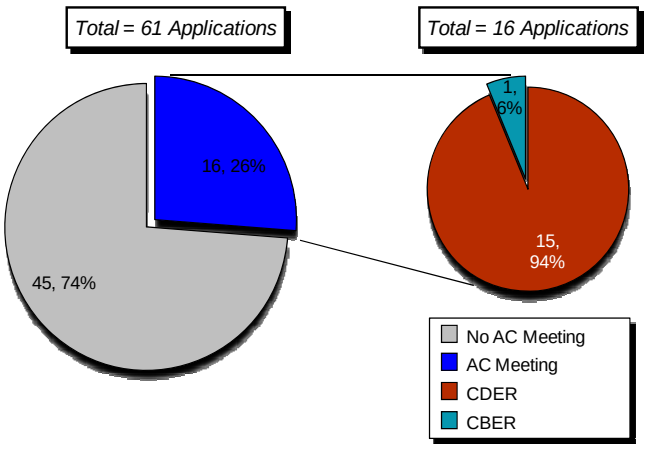
Many unique application-specific circumstances were also raised by review team members when describing the factors undermining timely completion of primary reviews. Given the variety of application-specific conditions that may arise over the course of a review to impact a review team's ability to complete primary reviews on time, process changes alone are unlikely to fully resolve the issue of non-adherence of this key GRMPs milestone.

For the four cohort applications that completed primary reviews on time, RPMs were asked to discuss any factors that they believe contributed to facilitating GRMPs adherence. In these cases, RPMs explained that leadership emphasized that these applications were the highest priority reviews in their divisions, which resulted in division review teams deprioritizing other applications to accommodate expedient review of these applications.

### 4.3.2. Advisory Committee (AC) Meeting Steps

GRMPs adherence was low for the five AC phase milestones, which include *Plan AC Meeting,*[78] *Disclose/Disseminate Applicant and FDA Background Materials,*[79] *Conduct AC Meeting,*[80] *Internal Meeting to Integrate AC Input*[81] and *Confidential Memo to AC to Announce Action.*[82] These steps were frequently conducted after the GRMPs milestone date and impacted the action date.

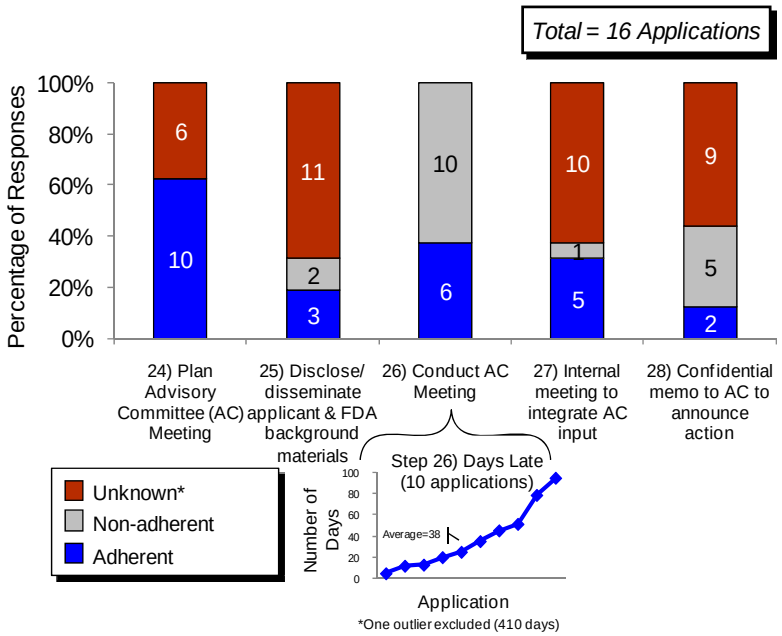
**Exhibit 43. Advisory Committee Meetings in Application Cohort and by Center**




As illustrated in Exhibit 43, 26% of (16/61) the applications in the study cohort included Advisory Committee meetings; one of these was held in CBER and the remaining 15 held in CDER. As depicted in Exhibit 44, 100% of application reviews adhered to the *Plan AC* step. Adherence levels were lowest (38%, 6/16) for adhering to the *Conduct AC Meeting* milestone. On average, non-adherent AC meetings were held 38 days late, ranging from a low of 5 days to a high of 94 days late. Of the 16 AC meetings held, six adhered with specified GRMPs milestone dates and did not appear to differ from non-adherent meetings by priority designation or review type.

[78] *Plan AC Meeting* milestone is not associated with a specific GRMPs timeframe. Rather, the milestone is met "when need is identified" and AC meeting is held (Exhibit 2).
[79] *Disclose/Disseminate Applicant and FDA Background Materials* milestone is 2 weeks before the AC meeting date for Standard/Priority reviews (Exhibit 2).
[80] *Conduct AC Meeting* milestone is end of month 8/5 for Standard/Priority reviews (Exhibit 2).
[81] *Internal Meeting to Integrate AC Input* milestone is 2 weeks after AC meeting for Standard/Priority reviews (Exhibit 2).
[82] *Confidential Memo to AC to Announce Action* milestone is at action for Standard/Priority reviews (Exhibit 2).

**Exhibit 44. GRMPs Adherence with Advisory Committee Meeting Action Milestones**




* Documentation for the AC planning and post-meeting steps is highly dependent on RPM records; "Unknown" indicates areas where RPM records were unavailable.

The key logistical challenges leading to low adherence of the *Conduct AC Meeting* activity were most often cited in RPM interviews and review discipline focus groups as a result of scheduling conflicts, competing products lists that must be provided from the review team, and clearance issues due to conflict of interest. Of these factors, the most frequently cited rationale as to why AC meetings were not held on time was the difficulty in coordinating schedules for panel members. The Division of Advisory Committee and Consultant Management (DACCM) staff at CDER and the Division of Scientific Advisors and Consultants at CBER coordinated scheduling of AC meetings and managed clearance of attendees, finding alternates if conflict of interest was an issue.

The RPMs and reviewers agreed that DACCM reliably schedules the meetings on the requested dates, however, the external factors cited above lead to low adherence to the GRMPs milestones. Due to scheduling conflicts, certain discipline reviewers have noted that the AC meeting frequently was scheduled at the end of the review cycle, interfering with holding a timely *Wrap-Up Meeting*. The timeliness of the AC meeting also appears to impact adherence with *Action*. Applications that comply with the AC meeting milestone are tied to higher adherence of final action with PDUFA goal dates. Conversely, AC meetings that were held late contributed to final actions completed after the PDUFA goal date. Data from interviews and focus groups suggest that the underlying driver for these results is that holding an AC meeting during the Action Phase causes other milestones to be delayed, impacting final action. Data from the FDA survey of RPMs, primary discipline reviewers, and review team supervisors indicate that scheduling an AC meeting has little impact on the late completion of primary reviews, as depicted in Exhibit 38. FDA review team members were asked in the survey to rank the factors that most frequently resulted in late completion of primary reviews, and only a small percentage of CDER (25%, 35/143) and CBER (15%, 9/62) respondents cited having an AC meeting as a primary factor affecting adherence to the GRMPs timeframe.

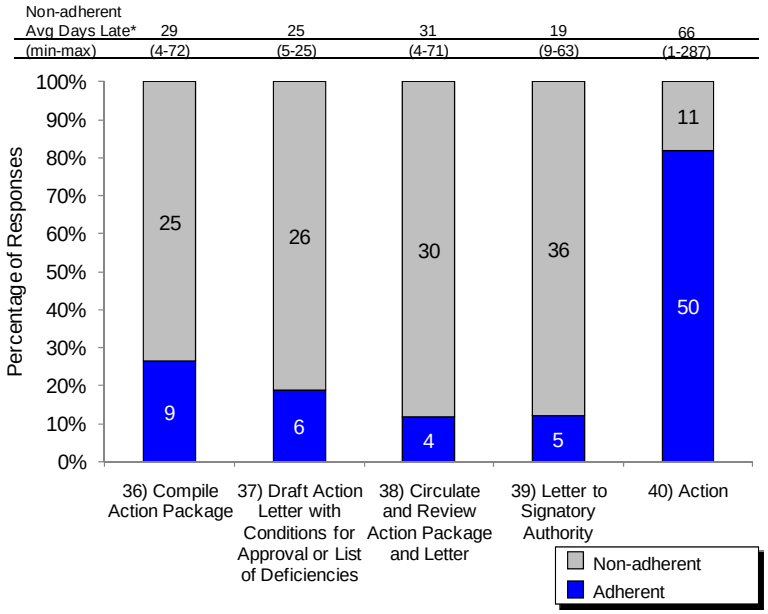
## 4.4. Detailed Findings for Selected Action Phase Milestones

Adherence to GRMPs final action steps are discussed in this section, including the following GRMPs milestones:

- *Compile Action Package* (Step 36)
- *Draft Action Letter with Conditions for Approval or List of Deficiencies* (Step 37)
- *Circulate and Review Action Package and Letter* (Step 38)
- *Letter to Signatory Authority* (Step 39)

GRMPs allow four to six weeks for completion of the four action milestones preceding final action (six weeks for standard reviews, four weeks for priority reviews). Analysis of cohort applications with available data points for these steps indicated that reviews met the GRMPs specified timeframes in only 12% (4/34) (*Circulate and Review Action Package and Letter*) to 26% (9/34) (*Compile Action Package*) of applications. Although non-adherence with each of the action steps preceding final action was greater than 70%, the final action step met the PDUFA goal date in 82% (50/61) of application reviews (Exhibit 45). Levels of adherence to GRMPs for the four action milestones preceding final actions were similar across CDER and CBER. Among non-adherent reviews, final steps (not including final action) were performed on average 19 to 31 days after the GRMPs-specified timeframe.

**Exhibit 45. GRMPs Adherence for Final Action Steps**



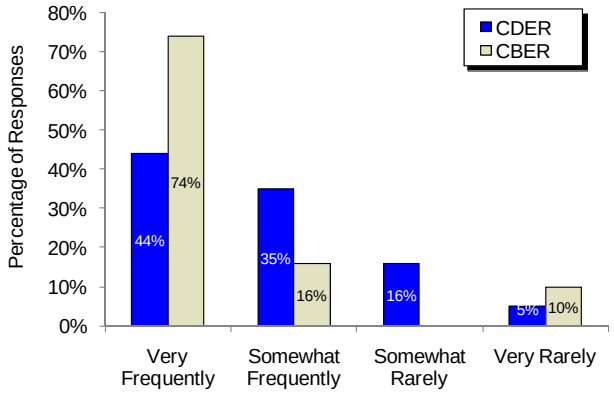

Sources: RPM Surveys (Steps 36, 37, 38, 39). DARRTS – Clinical Review memos, CDTL Review memos, Division/Office Director Summary Review (Steps 38, 39), Signatory Authority Memo Signature (Step 39), Complete Response or Action Letter stamp date (Step 40); Applications for which data was not found are excluded from this analysis.

The ability of review team members to initiate final action steps was highly dependent on timely completion of primary reviews. Late completion of primary reviews, which occurred in 92% (56/61) of cohort applications, compressed the timeframe available to complete final actions steps, resulting in high levels of non-adherence for initiating these activities (greater than 70%).

Only one review was fully compliant across all four action phase steps evaluated, and primary reviews for this application were completed on time.

The majority of CDER (44%, 24/55) and CBER (74%, 14/19) RPMs surveyed indicated that late completion of labeling has the biggest impact on lack of adherence with GRMPs final pre-action steps, as shown in Exhibit 46. This factor may have weighed in more heavily in survey responses than other potential responses, since all applications are required to submit a label for review.

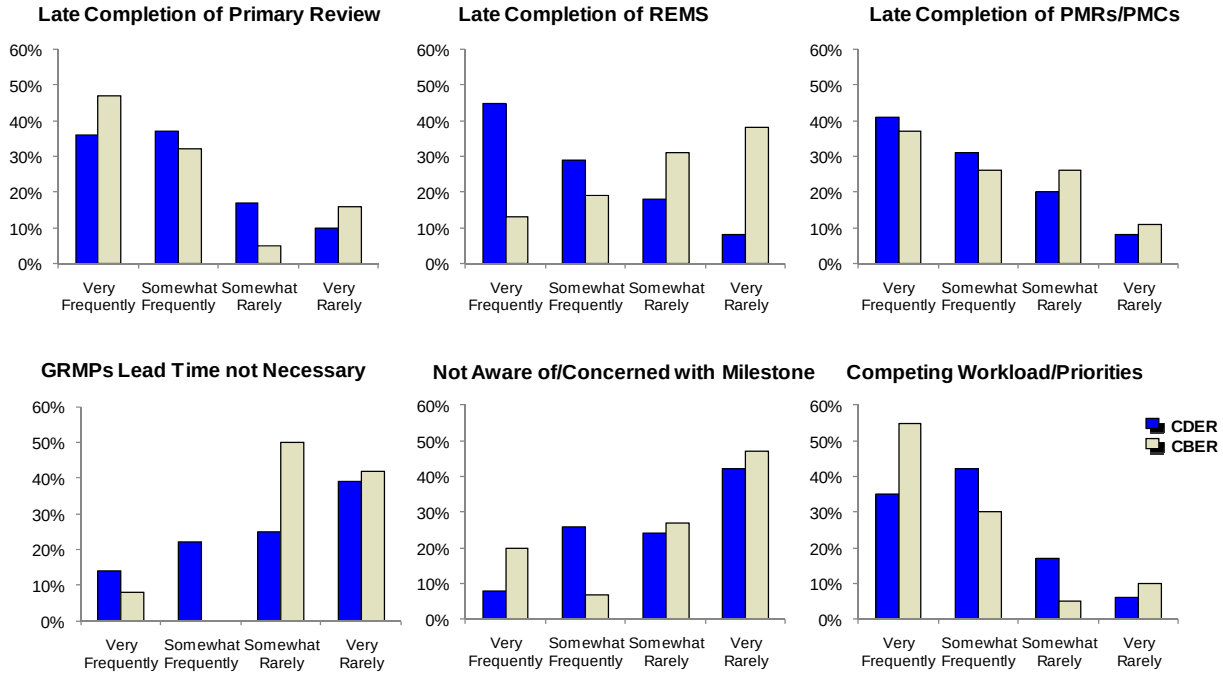
**Exhibit 46. Impact of Late Completion of Labeling on Adherence to GRMPs Pre-Action Milestones**




Source: FDA Survey, January 2011. "RPMs: *In your experience, what are the most frequent reasons why final pre-action steps are not done by the GRMPs-specified timeframe (e.g., compiling action package, circulating action package and letter for review, signatory authority sign-off)?"*

The frequency with which other factors assessed in the survey were thought to delay the final pre-action steps is depicted in Exhibit 47. In addition to late completion of labeling, late completion of primary reviews and competing workload or other priorities were major factors attributed by RPMs to low adherence with GRMPs-specified timeframes for final pre-action steps. Late completion of primary reviews is also a competing factor, since labeling discussions cannot begin until reviews are finalized, thereby delaying both of these GRMPs milestones that must be met before pre-action steps can occur. Many survey respondents commented that finalizing labeling and completion of primary reviews are highly interdependent and completion of final reviews often delays the completion of final labeling, which leads to delayed final pre-action steps.

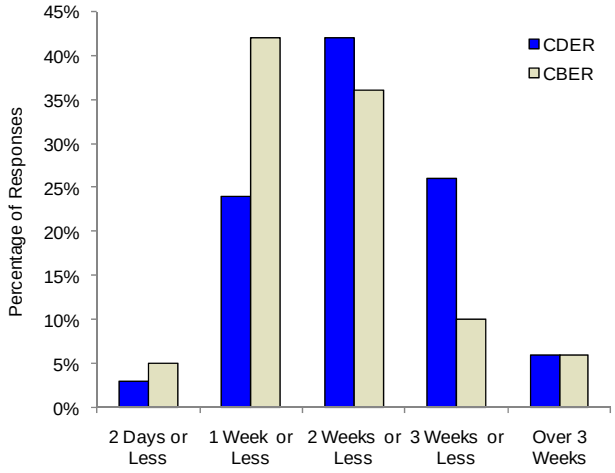
**Exhibit 47. Factors Impacting Adherence to GRMPs Pre-Action Milestones**




When asked if the lead time given in GRMPs is sufficient to complete the final action milestones, 84% (16/19) of RPM interview responses indicated that the lead time is either sufficient or unnecessary for completing the final action steps, while a minority of RPM interview responses (16%, 3/19) indicated that this compressed timeframe presented a challenge in completing the GRMPs final action milestones.

RPMs, primary discipline reviewers, and review team supervisors were surveyed to further assess views on the necessary amount of lead time for complete review of the action package before signoff. When asked how much time is necessary to give the signatory authority to thoroughly review the action package before signing off (i.e., lead time prior to PDUFA goal date for RPM to deliver action package/letter to signatory authority), the overall consensus was that the lead time necessary depends on the complexity of the application. As displayed in Exhibit 48, the majority of survey respondents perceived that 1 to 3 weeks was a sufficient amount of time for the signatory authority to review the action package before signoff.

**Exhibit 48. Review Team Perception of Time Needed for Signatory Authority to Review Action Package Before Signoff**




Source: FDA Survey, January 2011. "How much time do you believe is needed to give the signatory authority to thoroughly review the action package before signing off?"

RPMs interviewed commented that supervisors were kept apprised of the review progress through meetings and RPMs believed supervisors required less time than the 2-3 weeks allotted by GRMPs to review and finalize the action letter. Although a few RPMs stated that 2 to 3 weeks of lead time was necessary for supervisors to thoroughly review, provide comments on the action package, and sign off on the action package, many expressed that the specified lead time is unrealistic. Some RPMs suggested that one to two weeks was sufficient to perform final action steps and that the remaining time would be better allocated to discipline reviewers to complete their primary reviews. Among RPMs interviewed, the most frequently cited reason for late final action activities is that discipline reviewers use the time allocated to supervisory review and sign-off in order to complete their primary reviews. RPMs and discipline reviewers surveyed expressed similar sentiments and also indicated that 1 to 2 weeks of lead time was sufficient for reviewing the action package before signoff. Primary discipline reviewers, supervisors and team leaders were surveyed in both CDER and CBER to determine how long they believed the signatory authority needed to review the final action package before signoff, and the majority of review staff in both Centers believed that 3 weeks or less is sufficient. RPMs and discipline review team members are the primary agents responsible for transmitting completed reviews to the signatory authority, and the short amount of time perceived by review team staff to be acceptable for signatory review correlates with this step rarely occurring by the milestone date. Most RPMs and review team members perceived that the time allotted by GRMPs for completion of final action steps was sufficient; however, most (greater than 70%) applications in the cohort did not adhere to the GRMPs specified timeframes for each of the final pre-action steps and required on average an additional 3 to 4 weeks[83] to complete these steps.

[83] Among non-adherent reviews, final pre-action steps were performed on average 19 to 31 days after the GRMPs-specified timeframe, as displayed in Exhibit 45.

# 5. SUMMARY AND RECOMMENDATIONS

Booz Allen developed recommendations for process improvement by analyzing GRMPs implementation challenges described in the assessment of GRMPs adherence, and taking into account FDA and applicant process improvement suggestions that emerged through the root cause analysis. We are providing recommendations below in order of priority level, starting with those pertaining to specific GRMPs milestones that have the largest impact on adherence to GRMPs, followed by a broader set of recommendations and considerations that could improve GRMPs adherence in general.

## 5.1. Recommendations for Specific GRMPs Milestones

**Complete Primary Review – Add agenda item at mid-cycle meeting for disciplines to discuss and coordinate necessary review inputs**

The most frequently cited rationale as to why primary reviews are not completed on time is the failure among multiple review disciplines to coordinate review completion in an efficient and timely manner. Mapping of review interdependencies among disciplines revealed that all disciplines are interdependent on at least one other discipline to complete their primary reviews. However, clinical reviews have the highest number of and strongest level of dependencies on the inputs from all other discipline reviews. A mid-cycle meeting agenda that includes an item for each discipline to note required inputs would promote early coordination and initiation of any communication plans needed to share information to complete primary reviews. Drafts or near-complete versions of reviews could be planned for exchange between discipline reviewers, so that primary reviews across disciplines may be completed on or before the GRMPs milestone date.

**Request Consults – Identify standard consults**

RPMs and discipline reviewers noted ambiguity in identifying necessary consults for an application review. Center-wide identification during training of a clear set of “standard”, frequently occurring consults could eliminate delays during the early part of a review cycle to issue needed consults. The potential benefits of identifying “standard” consults is to increase the number of consult requests that could be initiated by RPMs within the first 45 days of the review, thereby affording consult reviewers longer lead-time to perform reviews. FDA survey findings indicated that the labeling/PPI consult were most frequently recognized by FDA staff as a standard consult and could be initiated earlier in the review cycle. However, OSE labeling reviewers (i.e., DMEPA, DRISK) report that they are often not invited to or informed of filing meetings and infrequently attend, so the need for labeling reviews is often determined late. Earlier and consistent inclusion of labeling consult reviewers at the filing meeting could facilitate timely identification of needed consults and decrease the amount of work compression for labeling reviews at the end of the review cycle.

A prominent recommendation that arose from CDER staff responses in the FDA survey included integrating consult requests into CDER data systems. Improvements in the system could allow RPMs to select and submit consult reviewer names, and reviewers could be automatically notified of the need to perform a consult review by requested completion timeframes. An electronic dropdown menu or checklist in FDA data systems of all available consult types, including an open text box area in the checklist, could allow RPMs to quickly check off needed consults, add in any specific application-specific directions in a free-type text box, and

automatically notify consult reviewers of requests. Such functionality could decrease the time and effort needed to generate consult requests on the part of RPMs, and could streamline the process needed to promptly notify appropriate consult reviewers.

**Hold Timely Meetings – Emphasize timely meeting milestones in training**

Failure to hold timely major meetings was in part due to the belief among most RPMs and discipline reviewers that meeting milestones need not be strictly interpreted. Given the work compression that is reported by discipline reviewers to occur at the end of the review cycle, and the finding that adherence levels for major meetings held near the end of the review cycle are lower than those held at the beginning of the review cycle, training on GRMPs that heighten awareness of and emphasize the importance of timely meetings, most notably at mid-cycle and wrap-up, could aid team collaboration efforts. Enforcement of timely meetings, combined with adequate meeting preparation on the part of discipline reviewers and RPMs, would relieve work compression closer to the action date and ensure that meetings are productive.

**Assign Review Team – Develop team assignment roster form**

Review team assignment dates currently entered into FDA data systems often do not accurately reflect the date that the reviewer is selected for the review team. Development and implementation of a team assignment roster form that is consistently used and completed by RPMs at the beginning of the review cycle to include discipline review team member names and assignment dates could improve the accuracy and reliability of this data going forward. For example, the roster form should include all review disciplines such as GXP/Facility reviewers (e.g., DSI, DMPQ, OCBQ), and labeling reviewers (e.g., OSE). Potential benefits of improving this process step include: allowing review team members to promptly receive notifications of the application review; enabling the correct review team members to be identified if application inquiries are necessary; reminding RPMs of all team members that should participate in meetings and have access to submission materials; improving the accuracy of future Center or Division assessments of GRMPs implementation. In lieu of using a team assignment roster form, RPMs may also choose to participate in the training program that would enable them to log reviewers and dates of assignment into FDA data systems directly.

**Identify Inspection Actions – Initiate identification of inspection actions prior to application filing**

Office of Compliance (OC) staff at CDER indicated in survey responses that earlier identification and communication of necessary manufacturing and clinical inspection actions prior to filing would improve timely completion of inspections. A consolidated and comprehensive list of inspection sites may be requested from applicants during clinical studies and/or pre-submission meetings, and potentially included as an agenda item for discussion (e.g., during End-of-Phase 2 meetings, pre-NDA/BLA meetings) so that FDA may identify potential domestic and foreign manufacturing and clinical facilities for inspections prior to application filing. Early and consistent notification and inclusion of OC staff at these meetings and early identification of sites could extend the timeframe OC would have available to schedule and complete timely inspections after submission, especially for priority review applications that require foreign inspections to be performed.[84] In addition, automation of applicant submission of manufacturing and clinical site information so that it may be readily accessible to OC would also speed and improve the

[84] Once the need for a foreign inspection is identified, the State Department requires at least 60 days lead time to process and approve requests for foreign travel. Additional time is needed to coordinate FDA inspections with applicants.

accuracy by which sites are identified and selected for inspections.[85] Applicants also indicated that late awareness and notification of requested inspections by FDA is a likely contributor to late scheduling and completion of inspections. Earlier engagement with and notification of manufacturers of necessary inspections would enable companies with variable production cycles to better anticipate and improve coordination of active production cycles, and permit FDA inspections to be more promptly scheduled and conducted.

## 5.2. General Recommendations to Improve GRMPs Implementation

Incomplete applicant submissions were commonly cited by FDA staff as a cause for missing GRMPs milestones, especially in later phases of the review cycle. Findings from FDA interviews, focus groups, and surveys indicated that a number of actions could improve overall quality of submissions that undergo a full review cycle. The recommendations made in this section are intended to assist FDA in improving the implementation and use of GRMPs to facilitate a more effective and efficient review process.

**Provide on-demand GRMPs training to CDER and CBER review staff –** A GRMPs training course was developed by FDA to educate FDA review staff on the GRMPs milestones. While most RPMs interviewed agreed that they were aware of GRMPs milestones, many CDER RPMs referred to formal training received from the 21st Century Review, and other RPMs reported learning about GRMPs through informal meetings and mentorship, and could not recall more specific training courses on GRMPs. Given the Center-specific differences discussed in Section 4.1 between CDER and CBER in formally operationalizing GRMPs, a GRMPs training and refresher course that is widely implemented across both Centers would set a baseline understanding of all GRMPs milestones among CDER and CBER review staff. FDA survey findings of review staff in CDER and CBER revealed a strong interest among staff to participate in a training or refresher course on GRMPs, and a belief that the course would have utility in improving adherence to milestones (Exhibit 11). Review staff also commented that training would be most helpful if made available online or as a searchable reference to allow real-time, on-demand access to materials.

**Update NDA/BLA submission guidance for industry –** On average, applications in the study cohort failed to adhere to 50% of milestone steps. Aside from late completion of primary reviews, many RPMs interviewed identified missing applicant data in the original submission as a key issue impacting adherence with these final action steps. One potential solution is to update existing draft and final guidances on the NDA/BLA submission process, including standard elements and content examples necessary for a complete application, in an effort to align existing guidances with the current FDA views on submissions. Applicants interviewed commented that they could not heavily rely on the draft guidances published by FDA because they were outdated, in some cases by more than ten years.

Applicants noted that guidances would be most helpful in areas where there is no regulatory precedent, such as novel therapeutic product areas, or in therapeutic areas or product classes where there is only one previously-approved drug. A few examples of guidances requested by applicants for development or to be updated include co-administration of vaccines, novel

[85] According to the Code of Federal Regulations (21 CFR 314.50), applicants must provide data on the name and locations of product use and manufacture.

adjuvants, and small molecule drugs; in addition, guidance on submission areas such as assay validation, stability data, and CMC data were also mentioned as potentially helpful.

Updated guidances would aid applicants in the submission process. Another benefit to FDA and applicants include minimizing incomplete application submissions and the need for a large number of information requests. Due to the effort required to update guidances, an immediate next step could be to prioritize guidances or applicant submission checklists that could be updated, either through identification of the most outdated or pivotal guidances. A less formal resource could be through development of a Frequently Asked Questions (FAQ) website to provide information on NDA/BLA submissions that are frequently raised by applicants.

**Better use of Refuse to File (RTF) authority –** In addition to assisting applicants with more current guidance, another potential solution is for the FDA review team to conduct a more thorough review early in the review cycle to identify missing data components by the filing meeting. Any deficiencies identified in data submissions could result in increased usage of RTF for incomplete applications and improve the quality of applications that undergo a complete review cycle. An RTF MaPP is currently in development by CDER that could assist review teams in determining the types of application deficiencies that could trigger RTF decisions.

**Provide specific timeframes for responses to information requests –** Missing applicant data could also be addressed if FDA issues specific timeframes on information requests (IR) to applicants. Applicant interviews indicated that clearer guidance on timeframes for expected responses would allow applicants to gauge the level of urgency with which responses should be submitted to FDA, and could improve FDA's ability to anticipate submission of missing data and coordinate review, especially near the end of the review cycle.

**Other FDA mechanisms and processes to ensure submission completion -** Applicants provided a number of suggestions to improve review cycle processes. One recommendation is to increase the use of the Applicant Orientation Presentation to conduct walk-throughs of newly-submitted applications. This GRMPs meeting step is optional and was infrequently held in the study cohort (8%, 5/61 applications). Moreover, 80% (4/5) of application reviews that included the Applicant Orientation Presentation held this meeting after the GRMPs milestone of 45/30 days for standard/priority reviews. However, applicants suggested that a meeting early in the review process to identify where key data is located in the application and to walk through areas of the submission could help prevent any misconceptions or confusion by the review team, and potentially decrease the need for subsequent information requests and amendments.

Applicants also mentioned during interviews that the application table of contents (TOC) is often developed many months prior to submission, and serves as a preview of the application components, structure, and level of detail intended for submission. Consistent and standard review of applicant TOCs during the pre-submission timeframe is one potential method of helping ensure early or prior to the review process that submission components are in place. Areas that FDA identifies as incomplete could then be raised to applicants prior to submission, enabling applicants time to make necessary changes upon submission.

Another suggestion that frequently emerged from applicant interviews is for FDA to provide earlier pre-submission meeting feedback to applicants. Applicants reported that pre-submission meetings are very helpful to anticipate and refine application submissions to be as thorough as possible, and that FDA consistently provides written feedback. Applicants believed that these meetings could be more helpful if written feedback to applicant questions were provided farther

in advance of the pre-submission meetings rather than one to two days prior to meetings, so that applicants would have adequate time to review FDA feedback, and discussions during the pre-submission meetings could be more targeted on other outstanding issues not already adequately addressed through written means.

# Appendix A: Interview Cohort

Application reviews that are included in the GRMPs assessment were evaluated based on a variety of factors, to ensure diversity in the product cohort. Applications from each Review Division/Office were included for documentation and analysis and a representative mix of the following factors were considered for selection and are summarized below, as well as in Exhibit 49. The distribution of the cohort in CDER and CBER is summarized in Exhibit 50.

- First Cycle Action within past 12 months (August, 2009 – July, 2010)
- All Review Divisions Represented
- NDAs / BLAs
- CDER / CBER Applications
- Original / Efficacy Supplements
- Planned Review Timelines Assessment Cohort (automatically included)
- Approved / Complete Response (First Cycle Action)
- Priority / Standard Reviews
- NMEs / Non-NMEs
- Minimize duplicative applicant companies
- Variety of product indications
- AC Meeting / No AC Meeting
- REMS (Including MedGuide) / No REMS

## Exhibit 49. Summary of GRMPs Study Application Cohort (61 Applications)

| Center | NDA/ BLA | App # | Seq # | Applicant Name | Product Name | Office/ Division | First Cycle Action | First Cycle Goal Date | P/S | NME | REMS | PMCs/ PMRs | AC Meeting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CDER | NDA | 22395 | 0 | NEUROGESX INC | QUTENZA (Capsaicin Patch 8%) | DAAP | AP | 11/16/09 | S | N | N | N | N |
| CDER | NDA | 21572 | 23 | CUBIST PHARMACEUTICALS INC | CUBICIN (DAPTOMYCIN INJ) | DAIOP | CR* | 06/01/09 | S | NA | N | N | N |
| CDER | NDA | 22288 | 0 | Ista Pharmaceuticals | Bepreve (Beptastine Besilate Ophthalmic Solution) | DAIOP | AP | 09/12/09 | S | Y | N | N | Y |
| CDER | NDA | 22187 | 1 | TIBOTEC INC | Intelence (TMC 125 ETRAVIRINE) | DAVP | AP | 11/23/09 | S | NA | N | Y | N |
| CDER | NDA | 22436 | 0 | MEDA PHARMACEUTICALS INC | ACYCLOVIR AND HYDROCORTISONE CREAM, 5%/1% TOPICAL (ME-609 cream) | DAVP | AP | 08/01/09 | S | N | N | Y | N |
| CDER | BLA | 125019 | 156 | Spectrum Pharmaceuticals, Inc. | ZEVALIN (ibritumomab tiuxetan) | DBOP | CR* | 07/02/09 | P | NA | N | Y | N |
| CDER | BLA | 125326 | 0 | GLAXO GROUP LIMITED D/B/A GLAXOSMITHKLINE #1809 | ARZERRA (Ofatumumab) | DBOP | AP | 10/31/09 | P | Y | Y | Y | Y |
| CDER | NDA | 22307 | 0 | ELI LILLY AND CO | Effient (Prasugrel Hydrochloride) | DCRP | AP | 09/26/08 | P | Y | Y | Y | Y |
| CDER | NDA | 20965 | 7 | DUSA PHARMACEUTICALS INC | LEVULAN KERASTICK (Aminolevulinic Acide HCL Solution) | DDDP | AP | 03/12/10 | S | NA | N | N | N |
| CDER | NDA | 22571 | 0 | SHIONOGI PHARMA INC | CUVPOSA ORAL SOLUTION (Glycopyrrolate Oral Solution, 1mg/5mL) | DDDP | AP | 07/28/10 | S | N | N | Y | N |
| CDER | NDA | 20449 | 59 | SANOFI AVENTIS US LLC | TAXOTERE (docetaxel) | DDOP | AP | 05/13/10 | P | NA | N | N | N |
| CDER | NDA | 22468 | 0 | ALLOS THERAPEUTICS INC | FOLOTYN (pralatrexate injection) | DDOP | AP | 09/23/09 | P | Y | N | Y | Y |
| CDER | NDA | 22511 | 0 | ASTRAZENECA LP | VIMOZO (PN 400 Naproxen/Esomeprazole Magnesium) | DGP | AP | 04/30/10 | S | N | N | Y | N |
| CDER | NDA | 22554 | 0 | SALIX PHARMACEUTICALS INC | XIFAXAN (Rifaximin) | DGP | AP | 03/24/10 | P | N | N | Y | Y |
| CDER | NDA | 22575 | 0 | SHIRE HUMAN GENETIC THERAPIES INC | VPRIV (VELAGLUCERASE ALFA FOR INJECTION) | DGP | AP | 02/28/10 | P | Y | N | Y | N |
| CDER | NDA | 22350 | 0 | BRISTOL MYERS SQUIBB CO | ONGLYZA (saxagliptin tablets, 2.5mg and 5 mg) | DMEP | AP | 07/30/09 | S | Y | N | Y | Y |
| CDER | NDA | 21425 | 17 | BAYER HEALTHCARE PHARMACEUTICALS | ULTRAVIST INJECTION (IOPROMIDE 300MGL/ML/370MGL/ML) | DMIP | CR* | 10/31/09 | S | NA | N | N | N |
| CDER | NDA | 22454 | 0 | GE Healthcare | DaTSCAN (Ioflupane I-123) | DMIP | CR* | 09/09/09 | P | Y | N | N | Y |
| CDER | NDA | 22555 | 0 | PHOTOCURE ASA | HEXVIX | DMIP | CR* | 12/30/09 | P | N | N | N | Y |
| CDER | NDA | 22009 | 2 | LOREAL USA PRODUCTS INC | ANTHELIOS 40 (3% ecamsule, 2% avobenzone, 10% octocrylene, 5% TiO2) (avobenzone/ecamsule/octocrylene/titanium) | DNCE | AP | 10/29/09 | S | NA | N | Y | N |
| CDER | NDA | 22470 | 0 | NOVARTIS CONSUMER HEALTH INC | NEXCEDE (ketoprofen oral – oral dissolving strips) | DNCE | AP | 11/26/09 | S | N | N | Y | N |
| CDER | NDA | 22565 | 0 | WYETH CONSUMER HEALTHCARE | Advil Congestion Relief (ibuprofen and phenylephrine) | DNCE | AP | 05/28/10 | S | N | N | Y | N |
| CDER | NDA | 22250 | 0 | ACORDA THERAPEUTICS INC | AMPYRA (Fampridine Tablets (DALFAMPRIDINE)) | DNP | AP | 01/22/10 | P | Y | Y | Y | Y |
| CDER | NDA | 22377 | 0 | KING PHARMACEUTICALS INC | ALSUMA (SUMATRIPTAN SUCCINATE AUTO-INJECTOR) | DNP | CR* | 05/17/09 | S | N | N | N | N |
| CDER | BLA | 125360 | 0 | MERZ PHARMACEUTICALS GMBH | XEOMIN (incobotulinumtoxinA) | DNP | AP | 08/01/10 | S | Y | Y | Y | N |
| CDER | NDA | 22352 | 0 | AR HOLDING CO INC | COLCRYS (Colchicine, USP, tablets, 0.6 mg) | DPARP | AP | 12/20/08 | P | N | Y | Y | N |
| CDER | BLA | 125276 | 0 | GENENTECH, INC. (Originally HOFFMAN-LA ROCHE) | ACTEMRA (TOCILIZUMAB) | DPARP | CR* | 09/18/08 | S | Y | Y | N | Y |

| Center | NDA/ BLA | App # | Seq # | Applicant Name | Product Name | Office/ Division | First Cycle Action | First Cycle Goal Date | P/S | NME | REMS | PMCs/ PMRs | AC Meeting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CDER | BLA | 125293 | 0 | Savient Pharmaceuticals | KRYSTEXXA (Pegloticase) | DPARP | CR* | 08/01/09 | P | Y | Y | Y | Y |
| CDER | BLA | 125338 | 0 | Auxilium Pharmaceuticals, Inc. | XIAFLEX (Clostridial Collagenase) | DPARP | AP | 10/15/09 | P | Y | Y | Y | Y |
| CDER | NDA | 22411 | 0 | LABOPHARM INC | Oleptro (TRAZODONE CONTRAMID OAD E-R CAPLET) | DPP | CR* | 07/18/09 | S | N | Y | N | N |
| CDER | NDA | 22430 | 0 | FERRING PHARMACEUTICALS INC | LYSTEDA (tranexamic acid) | DRUP | AP | 10/30/09 | P | N | N | Y | N |
| CDER | NDA | 22404 | 0 | BioAlliance Pharma | Oravig (Miconozole buccal tablets) | DSPTP | AP | 04/16/10 | S | N | N | Y | N |
| CDER | NDA | 50824 | 0 | DAVA PHARMACEUTICALS INC | TTBN (OMEPRAZOLE 25MG/AMOXOCILLIN 500MG/CLARITHROMYCIN 500MG) | DSPTP | CR* | 07/22/10 | S | N | N | N | N |
| CBER | BLA | 103174 | 5520 | Talecris Biotherapeutics, Inc. | PROLASTIN-C (Alpha-1-Proteinase Inhibitor (Human)) | OBRR | AP | 10/17/09 | S | NA | N | Y | N |
| CBER | BLA | 125325 | 0 | KAMADA LTD. #1826 | GLASSIA (Alpha-1-Proteinase Inhibitor (Human)) | OBRR | AP | 07/01/10 | S | Y | N | Y | N |
| CBER | BLA | 125329 | 0 | BIO PRODUCTS LABORATORY | GAMMAPLEX (Immune Globulin Intravenous (Human)) | OBRR | AP | 09/17/09 | S | Y | N | Y | N |
| CBER | BLA | 125350 | 0 | CSL Behring AG | Hizentra 15ml fill (Immune Globulin Subcutaneous (Human), 20% Liquid) | OBRR | AP | 02/28/10 | S | Y | N | Y | N |
| CBER | BLA | 125351 | 0 | Nycomed Danmark ApS | TachoSil (Fibrin Sealant Patch) | OBRR | AP | 04/05/10 | S | Y | N | Y | N |
| CBER | BLA | 103606 | 5374 | MERCK & CO., INC. | VAQTA (HEPATITIS A VACCINE INACTIVATED) | OVRR | CR* | 02/14/10 | S | NA | N | N | N |
| CBER | BLA | 125108 | 341 | Merck & Co., Inc. | PROQUAD (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) | OVRR | AP | 10/29/09 | S | NA | N | N | N |
| CBER | BLA | 125300 | 0 | NOVARTIS VACCINES AND DIAGNOSTICS, INC. | MENVEO (MENINGOCOCCAL [GROUPS A, C, Y, AND W 135] OLIGOSACCHARIDE DIPHTHERIA CRM197 CONJUGATE VACCINE) | OVRR | CR* | 06/29/09 | S | Y | N | Y | N |
| CBER | BLA | 125347 | 0 | GlaxoSmithKline Biologicals | HIBERIX (Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)) | OVRR | AP | 09/16/09 | P | Y | N | Y | N |
| *Information was redacted from the applications below to protect confidentiality. | | | | | | | | | | | | | |
| | | | | | | | CR | | S | N | N | N | N |
| | | | | | | | CR | | S | N | Y | N | N |
| | | | | | | | CR | | P | Y | N | N | Y |
| | | | | | | | CR | | P | Y | N | N | Y |
| | | | | | | | CR | | S | N | N | N | N |
| | | | | | | | CR | | S | Y | Y | N | N |
| | | | | | | | CR | | S | Y | N | N | N |
| | | | | | | | CR | | S | Y | N | N | N |
| | | | | | | | CR | | S | Y | N | N | Y |
| | | | | | | | CR | | S | Y | Y | N | N |
| | | | | | | | CR | | S | N | N | N | N |
| | | | | | | | CR | | S | NA | N | N | N |
| | | | | | | | CR | | P | NA | N | N | N |
| | | | | | | | CR | | S | N | N | Y | N |
| | | | | | | | CR | | S | NA | N | N | N |
| | | | | | | | CR | | P | Y | N | N | N |

| Center | NDA/ BLA | App # | Seq # | Applicant Name | Product Name | Office/ Division | First Cycle Action | First Cycle Goal Date | P/S | NME | REMS | PMCs/ PMRs | AC Meeting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CR | | S | Y | N | N | Y |
| | | | | | | | CR | | S | Y | N | N | N |
| | | | | | | | CR | | S | N | Y | N | N |

*Application has since been approved.

**Exhibit 50. Full Study Cohort Distribution in CDER and CBER Review Divisions/Offices**

| CDER Office | Division | No. of Applications (49; 42 NDAs, 7 BLAs) |
|---|---|---|
| **ODEI (9)** | DCRP | 2(O) |
| | DNP | 5(O)* |
| | DPP | 2(O) |
| **ODEII (9)** | DMEP | 2(O) |
| | DPARP | 5(O)** |
| | DAAP | 1(O), 1(S) |
| **ODEIII (9)** | DGP | 4(O) |
| | DRUP | 2(O |
| | DDDP | 1(O), 2(S)* |
| **ODEIV (8)** | DNCE | 3(O),1(S) |
| | DMIP | 3(O), 1(S) |
| **Antimicrobial (7)** | DAVP | 1(O), 1(S) |
| | DAIOP | 2(O), 1(S) |
| | DSPTP | 2(O) |
| **Oncology (7)** | DDOP | 2(O), 1(S) |
| | DHP | 1(O), 1(S) |
| | DBOP | 1(O)*, 1(S)* |

* One of these applications is a BLA
** Three of these applications are BLAs

| CBER | No. of Applications (12 BLAs) |
|---|---|
| **Original BLA** | 9 |
| **Supplement BLA** | 3 |

# Appendix B: FDA Interview Guide for Regulatory Project Managers (RPMs)

| | |
|---|---|
| General GRMPs Questions | 1) Are you aware of the GRMPs timeframes?<br>2) Did you participate in any training on the GRMPs? If so, how would you assess the training?<br>3) Do you use the 21st Century Review scheduling planner to set/meet milestones?<br>4) Do you perceive that all the internal milestones (e.g., review team assignment, hold filing/planning meetings, complete primary reviews) are important to meet by GRMPs timeframes? Which ones are most important? Why?<br>5) Are you held accountable or do you hold others accountable for meeting non-PDUFA milestones? If so, how?<br>6) How do the GRMPs impact the review?<br>7) Are they helpful? What about them is not helpful? |
| Acknowledge Application Receipt in Writing<br><br>***Compliant or Non-compliant*** | 8) Are there any decisions or pre-requisites for sending the acknowledgement letter?<br>9) In your case, why was the acknowledgement letter not sent by the GRMPs-specified timeframe? ***[Non-compliant Only] – follow up as necessary to root cause.***<br>10) Do you perceive any cultural or staff-induced factors that contribute to the delay in issuing an acknowledgement letter to the sponsor?<br>***[Non-compliant Only]*** |
| Review Team Assignment<br>• Step 4) Assign Review Team<br><br>***Compliant or Non-compliant*** | *11)* In your case, what caused the delay in assigning review team members? ***[Non-compliant Only]- follow up as necessary to root cause.***<br>12) Is there a standard timeframe by which RPMs log review team members into IT systems or notify document room staff?<br>13) Do you perceive this to be an important milestone to meet? Why or why not?<br>14) Are there any technological barriers to logging reviewers into the system on time? |

| | |
|---|---|
| Complete Primary Reviews<br><br>***Compliant or Non-compliant*** | 15) How do you define timely completion of primary reviews (e.g., logged into DARRTS by a certain date)?<br><br>16) Do RPMs or Team Leaders undertake any specific management approaches or activities (e.g., reminders) to enforce timely submission and log-in of primary reviews?<br><br>17) In your case, why was the primary review not completed by the GRMPs-specified timeframe?<br><br>18) Do you perceive this to be an important milestone to meet? Why or why not? |
| Internal Meetings<br>• Step 9) Holding Filing Meeting;<br>• Step 14) Conduct Planning Meeting;<br>• Step 19) Mid-cycle Meeting<br>• Step 29) Wrap-up meeting<br>• Step 31) Pre-approval Safety Conference<br><br>***Compliant or Non-compliant*** | 19) How far in advance do you typically begin scheduling the filing meeting? (planning meeting, mid-cycle meeting, wrap-up meeting)?<br><br>20) How do you determine when to schedule the meeting?<br><br>21) Is there an organizational expectation that attendance for all review disciplines at these key meetings is important?<br><br>22) In your case, why was the [filing, planning, midcycle, wrap-up] meeting not held by the GRMPs milestone date? ***[Non-compliant only]***<br><br>23) What barriers prevent timely filing/planning/mid-cycle/wrap-up meetings from occurring? ***[Non-Compliant Only]*** |
| Internal Consults<br>• Step 10) Request Consults – ***Compliant or Non-compliant***<br>• Step 11) Identify Inspection Actions – ***Compliant or Non-compliant*** | 24) What are the barriers to timely issuance of standard consults? ***[Non-Compliant Only]***<br><br>25) What processes, tools, and/or behaviors contribute to timely consult requests? ***[Compliant Only]***<br><br>26) Which types of consults are difficult to predict a need for until in-depth reviews occur?<br><br>27) Are there any reasons for which consult requests are identified but deliberately held off or postponed? If so, what?<br><br>28) How and when do the appropriate review team members notify the RPM of inspection actions needed?<br><br>29) Is the identification of inspection actions routinely discussed during the filing meeting?<br><br>*30)* In your case, why were inspection actions identified after the GRMPs milestone date? ***[non-compliant only]***<br><br>31) Why might BLA inspection actions be identified later than for NDAs? ***[BLAs Only]*** |

| | |
|---|---|
| Advisory Committee Meeting<br>• Step 26) Conduct AC Meeting<br><br>***[Only if AC meeting held] Compliant or Non-compliant*** | 32) When is the AC meeting scheduled?<br><br>33) What are the key logistical or technological challenges to coordinating an AC meeting on time? (e.g., timing, clearance) ***[Non-Compliant Only]***<br><br>34) Are there any people/cultural challenges to coordinating an AC meeting on time? If so, what? ***[Non-Compliant Only]***<br><br>35) What processes, tools, and/or behaviors do you believe contribute to a timely AC meeting? ***[Compliant Only]*** |
| Final Action Steps<br>• Step 36) Compile Action Package<br>• Step 37) Draft Action Letter<br>• Step 38) Circulate and Review Action Package and Letter<br>• Step 39) Letter to Signatory Authority<br>• Step 40) Action<br><br>***Compliant or Non-compliant*** | 36) Do you perceive that earlier completion of primary reviews would improve compliance with the final pre-action steps? ***[Non-Compliant Only]***<br><br>37) What processes, behaviors, and/or other review steps contribute to timely completion of the final action steps? ***[Compliant Only]***<br><br>38) In your case, why were these final steps leading up to action not completed by the GRMPs-specified timeframe? ***[Non-Compliant Only]***<br><br>39) Is the amount of lead time in the GRMPs really necessary?<br><br>40) What are the most significant drawbacks of the limited time to completing pre-action steps? |
| Planned Review Timelines<br>• Include target date for initiating discussions of PMRs/PMCs and labeling – ***Compliant or Non-compliant***<br>• Initiate PMR/PMC and labeling discussions by the target date – ***Compliant or Non-compliant (labeling and/or PMC)*** | 41) Did you participate in training on implementation of planned review timelines processes?<br><br>42) Why were planned review timelines for labeling and PMR/PMC discussions not included in the filing communication letter? ***[Non-Compliant Only]***<br><br>43) In your case, why were labeling and/or PMR/PMC discussions not initiated by the target date specified in the filing communication? ***[Non-Compliant Only]***<br><br>44) What could be improved in the process or tools available that would help to meet the target dates for initiating these discussions with the sponsor? ***[Non-Compliant Only]***<br><br>45) What specific FDA processes or behaviors would you attribute to initiating timely labeling or PMR/PMC discussions with the sponsor? Can you identify any sponsor behaviors that might also contribute to timely discussions? ***[Compliant Only]*** |

# Appendix C: FDA Discipline Reviewer Focus Groups and Discussion Guide

| Summary of Focus Group Types (10) | Participants (49) |
|---|---|
| CBER Product Quality Reviewers | 4 |
| CBER Clinical Pharmacology Reviewers | 2 |
| CBER Clinical Reviewers | 4 |
| CBER Non-Clinical Reviewers | 1 |
| CBER Biostatistics Reviewers | 5 |
| CDER Product Quality Reviewers | 6 |
| CDER Clinical Pharmacology Reviewers | 8 |
| CDER Clinical Reviewers | 3 |
| CDER Non-Clinical Reviewers | 7 |
| CDER Biostatistics Reviewers | 9 |

## Focus Group Discussion Guide

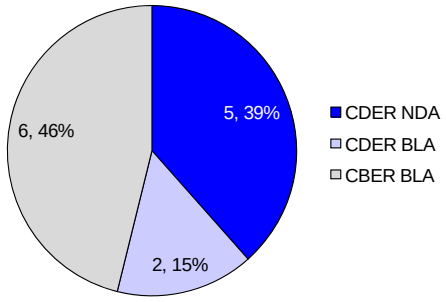
| | |
|---|---|
| General GRMPs Questions | 1) What are the GRMPs milestones that you are responsible for meeting?<br>2) Do you perceive that all the GRMPs milestones for which you are responsible are important to meet by GRMPs timeframes?<br>3) How has the review process changed since the implementation of the GRMPs? Is there anything about the GRMPs that is not helpful?<br>4) Are you held accountable for meeting these milestones? If so, how?<br>5) How are you assigned to an NDA/BLA? Is this effective? |
| Discussion of Selected GRMPs Milestones | 6) Do the GRMPs allow for sufficient time to review the application to determine whether it is fileable?<br>7) Do you think all the milestone meetings are helpful to the review process (filing/planning/mid-cycle/wrap-up)? Why or why not?<br>8) How do you define completion of the primary review?<br>9) What other activities or inputs (e.g., other discipline reviews) are often required for you to complete your review? What activities are dependent on the completion of your review?<br>10) Why are primary reviews so rarely completed by the GRMPs timeframe?<br>11) How do Advisory Committee meetings impact the timeframe by which primary reviews are completed?<br>12) Is there anything that would facilitate more timely completion of the primary review? |
| Recommendations to Increase GRMPs Compliance | 13) Are there any processes, tools, or behaviors that would improve GRMPs compliance across the discipline reviews? |

# Appendix D: Applicant Characteristics and Interview Guide

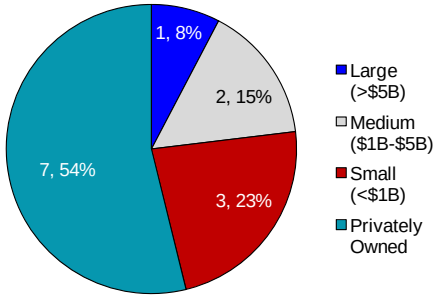
Applicant companies were selected from the study cohort to participate in one hour interviews to discuss their perspectives on GRMPs implementation and to offer suggestions for improvement. Senior regulatory officials from 13 companies participated in these interviews. A representative mix of the following characteristics was considered for applicant selection and is summarized below in Exhibit 51.

**Exhibit 51. General Characteristics of Applicants Interviewed for GRMPs Study (13 Companies)**

**Type of Application Submitted by Applicant Company**




**Applicant Participants by Company Size***




* Company size is determined for publicly traded companies based on market capitalization on January 1, 2010.

**Other Cohort Application Characteristics of Applicant Companies Interviewed**

| Priority/Standard | AC Meeting Held | Planned Review Timelines (PRT) Cohort | PRT Notification Met | Approval/CR |
|---|---|---|---|---|
| 46% (6/13) Priority | 38% (5/13) | 85% (11/13) | 77% (10/13) | 46% (6/13) Approved |

## Background Questions

1) How would you describe your awareness and understanding of the following aspects of GRMPs?
   a. Expectations of industry
   b. FDA review timelines

2) In your experience, what, if any, differences in the CDER/CBER application review process have been most observable since GRMPs were implemented (i.e., over the last several years)?

## General Application Experience

3) For the NDA/BLA(s) that you have submitted, do you typically solicit FDA input throughout early planning and product development phases (i.e., for clinical trials, input on protocols)?

4) Do you routinely request or participate in pre-NDA/BLA meetings with FDA when preparing submission of an NDA/BLA?

a. If so, how helpful are these meetings in terms of preparing your company for a complete submission?

   i. Not helpful
   ii. Slightly helpful
   iii. Moderately helpful
   iv. Very helpful
   v. N/A – we do not typically hold pre-NDA/BLA meetings with FDA in preparing submissions

b. In what ways are these meetings helpful? How could they be more helpful?

c. Are there any reasons why your company does not incorporate certain feedback provided by CDER/CBER from these meetings into your company's application submission? Please elaborate.

5) How helpful is FDA guidance to industry on new drug/biologics submissions?

   i. Not helpful
   ii. Slightly helpful
   iii. Moderately helpful
   iv. Very helpful
   v. N/A – we have not referred to FDA guidance to industry in preparing submissions

6) What additional information from CDER/CBER would be helpful to your company to enable a thorough and complete product submission?

7) Does your company use or refer to a standard template(s) when composing a new drug/biologics license application, in terms of application structure, content sections, and format?

   i. Yes, we have standard templates for all types of applications
   ii. No, we do not use standard templates

b. If so, is this template(s) developed by your company?

   i. Yes, please describe _____
   ii. No, please describe _____

c. If not, how do you decide how to develop/structure/compile your application package for submission?

8) Does your company currently prepare NDA/BLA application submissions to the FDA as electronic or paper/mixed files?

   i. Electronic only
   ii. Mixed (Electronic/Paper)
   iii. Paper only

9) If your company does not exclusively submit electronic applications, what barriers prevent your company from doing so?

   i. No barriers, we use electronic submissions exclusively
   ii. Lack of company/staff experience with full electronic submissions
   iii. Lack of company resources to invest in electronic submission tools
   iv. Other, please describe _____

10) What factors prevent your company from making complete submissions of data packages to the FDA at the time of initial submission?

11) Does your company routinely provide FDA with accurate timelines for submission of planned amendments and safety updates in advance of these submissions?

12) Does your company abide by any standard internal timelines or tracking tools to ensure timely responses to FDA information requests?

    a. If so, what timelines or tools are used? (e.g., no more than 30 days, tracking tools)

    b. How many days does it typically take for your company to respond to an FDA information request?

    c. What variables impact the time to respond to an information request?

13) In your opinion, does FDA provide sufficient guidance to sponsors on when it expects to receive a response from your company regarding an information request?

14) Does your company typically send individual amendments/responses to each FDA information request or consolidate responses to multiple FDA information requests in a single amendment submission?

    i. Individual
    ii. Multiple
    iii. Other, please describe _____

15) Does your company use any external sources to obtain and analyze clinical data?

    a. If so, does your company find it more difficult to promptly coordinate responses to FDA requests for information? Please elaborate.

## Planned Review Timelines

16) Is your company aware of the new planned review timeline requirements as mandated by FDAAA which requires FDA to:

    a. notify sponsors via the 74-day letter of the timeframe by which labeling and/or PMR/PMC discussions will be initiated?

    b. begin labeling and/or PMR/PMC discussions by the indicated timeframe?

17) Has implementation of the planned review timelines impacted your company's processes for preparing submissions to FDA?

    a. If so, how?

18) Do discussions with FDA regarding labeling, PMR/PMCs, and/or REMS begin during the timeframe indicated to your company by FDA in the 74-day filing communication letter?

19) Do you ensure that your company's labeling submissions are complete or finalized for FDA review by these dates?

    a. What actions are taken by your company to ensure timely completion/finalization of labeling submissions?

    b. What actions are taken by your company when preparing labeling submissions to minimize further FDA information requests and need for data?

20) What factors prevent your company from being able to finalize/complete labeling by the date when discussions are supposed to begin with FDA?

21) How do you decide what data to include in or exclude from your application?

22) Are there any processes that your company takes to ensure that FDA has adequate time to review and finalize labeling and PMR/PMCs? If so, please describe?

## Application-Specific Questions

23) Analysis of **[Insert NDA/BLA Number and Product Name]** indicated that a **[large/small]** number of information requests were issued by FDA to your company.

    a. What were the reasons behind the large number of information requests? **[>15 information requests only]**

    b. What actions does your company take to mitigate the need for FDA to issue requests for information and more data and to facilitate first cycle approval?

24) Analysis of **[Insert NDA/BLA Number]** submitted by your company indicated that **[CDER/CBER]** had missed the GRMPs milestone regarding the completion of primary review (end of month 8 for standard applications, end of month 5 for priority applications). What actions could your company have taken to facilitate **[CDER/CBER's]** compliance with this milestone? **[Non-compliant primary review only]**

25) Do you believe there was sufficient time for a reasonable discussion/negotiation of labeling for **[Insert NDA/BLA Number]**?

26) Do you believe there was sufficient time for a reasonable discussion/negotiation of PMRs/PMCs for **[Insert NDA/BLA Number]**?

# Appendix E: Respondent Characteristics and Survey Questions for FDA Online Surveys

FDA staff surveys were developed to refine initial findings and themes from RPM interviews and discipline reviewer focus groups. Three surveys were administered online using the SurveyMonkey tool in January 2011. The first of the three surveys was administered to discipline reviewers, RPMs, and supervisors/team leaders in CDER (Office of New Drugs, Office of Pharmaceutical Science and Office of Translational Science) and CBER, and yielded a total of 409 responses.

The latter two surveys were administered to the Office of Surveillance and Epidemiology (OSE), which yielded 17 responses, and the Office of Compliance (OC), which yielded 24 responses.

Survey participant characteristics and survey questions are included in the sections below.

**Exhibit 52. Respondent Characteristics for FDA Review Team Survey**

**A. Type of Application Submitted by Applicant Company**

| Application Type Submitted | Percent of Applicant Companies |
|---|---|
| CDER NDA | 39% (5/13) |
| CDER BLA | 15% (2/13) |
| CBER BLA | 46% (6/13) |

**B. Applicant Participants by Company Size**

| Company Size | Percent of Applicant Companies |
|---|---|
| Large (>$5B) | 8% (1/13) |
| Medium ($1B-$5B) | 15% (2/13) |
| Small (<$1B) | 23% (3/13) |
| Privately Owned | 54% (7/13) |

**C. Other Cohort Application Characteristics of Applicant Companies Interviewed**

| Priority/ Standard | AC Meeting Held | Planned Review Timelines Cohort | Planned Review Timelines Notification Met | Approval/CR |
|---|---|---|---|---|
| 46% (6/13) Priority | 38% (5/13) | 85% (11/13) | 77% (10/13) | 46% (6/13) Approved |

## E.1 FDA Review Staff Survey

### Introduction and Demographic Information

In support of the PDUFA IV Reauthorization Performance goals, FDA has contracted with the management consulting firm Booz Allen Hamilton to analyze the Good Review Management Principles and Practices (GRMPs) compliance in CDER and CBER. The objectives of this study are to determine the degree of implementation of GRMPs and to identify root causes for areas of low compliance that can be addressed to improve the review process.

This brief validation survey is being provided to FDA review team members, including RPMs, discipline reviewers, and review team supervisors, to refine and further validate preliminary findings and key themes that have emerged from the study's initial phases of evaluation. Your participation is an important part of the overall Assessment of GRMPs Implementation Study.

Please note that your responses are anonymous and confidential. If you have questions regarding the survey or project, please email the Contracting Officer's Technical Representative, Bill Hagan.

For all questions, please consider your experience with NDA/BLA reviews over the prior two years only. Certain questions only apply to particular roles, as noted, and can be ignored by those for whom they are not applicable. The entire survey should take approximately 10 minutes to complete for reviewers and 20 minutes to complete for RPMs. Thank you for taking the time to participate in this survey, we appreciate your feedback and comments.

1) In which Center do you currently work?

2) Please describe your role in the NDA/BLA review process.

3) How many years have you worked in this role at the FDA?

4) If applicable, please select your OND review division or CBER review office.

5) How likely do you believe it is that GRMPs compliance would be improved if periodic refresher trainings on the GRMPs were made available to RPMs, discipline reviewers and team leaders?
   ☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

6) How likely would you be to attend a one-time or refresher training on GRMPs milestones if it were made available?
   ☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

7) How likely do you believe it is that compliance with GRMPs would improve if review team members were assessed on meeting their relevant GRMPs milestones (e.g., attendance at major review meetings, timely completion of primary review) in an annual performance review?
   ☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

8) For each GRMPs milestone listed below, what do you believe is an acceptable timeframe for completion with respect to the deadline specified in the GRMPs guidance?

   - Assign Discipline Reviewers
   - Hold Filing/Planning Meeting
   - Identify Clinical Site Inspection Actions
   - Conduct Mid-Cycle Meeting
   - Complete Primary Review

- Conduct Wrap-Up Meeting
- Initiate Labeling Review and Discussions
- Initiate Negotiations of PMRs/PMCs
- Circulate Action Package and Letter
- Send Action Letter to Signatory Authority
- Take Action

Please provide any additional comments you may have about this question.

## Filing Determination and Review Planning Phase

9) RPMs only – Which one of these choices most closely describes your typical practice on review team assignment?

- ☐ I enter each review team member into DARRTS as soon as they are assigned to the application
- ☐ I enter all review team members into DARRTS only after all team members have been assigned
- ☐ I send individual reviewer names to the Document Control Room as soon as each member is assigned
- ☐ I send a list of all reviewer names in one e-mail to the Document Control Room only after all team members are assigned

Please provide any additional comments you have on this question.

10) Team Leaders/Supervisors Only – Which of the following factors do you take into account when determining a reviewer to assign to an application? Please mark all that apply.

- ☐ PDUFA goal date and timeframe for review (NDA vs. IND)
- ☐ Number of data files submitted in an application
- ☐ Number of trials submitted in an application
- ☐ Reviewer's current workload
- ☐ Reviewer's previous experience with applicant/sponsor Reviewer's previous experience with therapeutic area
- ☐ Other (please specify)

11) RPMs Only – Which one of the following two practices most closely approximates how you typically schedule each of the major milestone meetings listed?

| | Schedule shortly after review team is assigned | Schedule during the review cycle as the milestone approaches |
|---|---|---|
| Filing/Planning Meeting | ☐ | ☐ |
| Mid-Cycle Meeting | ☐ | ☐ |
| Wrap-Up Meeting | ☐ | ☐ |

Please provide any additional comments you have on this question.

12) RPMs Only – Which consults do you consider to be "standard" (i.e., those consults that can be routinely identified and issued at or before the filing/planning meeting)? Please mark all that apply.

- ☐ Trade name/PPI
- ☐ Environmental Assessment
- ☐ Claims of Categorical Exclusion
- ☐ Abuse Potential
- ☐ Pregnancy Labeling
- ☐ Health-related Quality of Life
- ☐ Postmarketing items (e.g., REMS and PMRs/PMCs)
- ☐ Others (please specify)

13) RPMs Only – For consults that you consider to be "standard" or frequently occurring, what are the typical reasons for which consults are requested late? Please mark all that apply.
- ☐ Insufficient information at time of filing meeting
- ☐ Reviewers do not notify RPM of need for consult request until later in review process
- ☐ Administrative delays
- ☐ RPM did not request consults from reviewers in advance of filing meeting
- ☐ Not necessary to issue requests by GRMPs milestone
- ☐ Others (please specify)

14) RPMs Only – How likely do you believe it is that consult requests would be issued on a more timely basis (i.e., in compliance with GRMPs milestone of within 45 days of application receipt) if this task were a standard agenda item during filing meetings?

☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

15) RPMs Only – How likely do you believe it is that GRMPs compliance with requesting standard consults would improve if you were provided a list of "standard" frequently-occurring consults that could be routinely issued at or before the filing meeting?

☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

Please provide any additional comments you have about this question.

16) RPMs Only – In your experience, what are the most common reasons why inspection requests are issued late?
- ☐ Not a standard item on the filing meeting agenda
- ☐ Review team members do not identify need until later in review process
- ☐ RPM delays in issuing the inspection requests on timely basis
- ☐ Inspection (facility) reviewer assigned late
- ☐ Difficulty coordinating with DSI
- ☐ Applicant provided insufficient information about inspection sites
- ☐ Not applicable – in my experience inspection requests have always been timely
- ☐ Others (please specify)

17) How likely do you believe it is that setting a discrete deadline (milestone) for the completion of inspection actions would improve the review team's ability to complete primary reviews on time?

☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

Please add any additional comments you have about this question.

18) How effectively do you think your office/division currently exercises its refuse to file (RTF) decision for applications that are discovered to have deficiencies before filing?
- ☐ Very Effectively
- ☐ Somewhat Effectively
- ☐ Somewhat Ineffectively
- ☐ Very Ineffectively

Please provide any additional comments you have about this question.

19) How likely do you believe it is that compliance with GRMPs milestones would improve for application reviews if FDA more effectively exercised refuse to file (RTF) decisions for certain applications?

☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

## Review Phase

20) In your experience, what explains why any of the major meeting milestones listed below does not take place by its GRMPs-specified timeframe? Please check all that apply.

| | Filing/Planning Meeting | Mid-Cycle Meeting | Wrap-up Meeting |
|---|---|---|---|
| Scheduling conflicts | ☐ | ☐ | ☐ |
| Lack of sponsor responsiveness | ☐ | ☐ | ☐ |
| Not aware of GRMPs milestone | ☐ | ☐ | ☐ |
| Use of scheduling tool that does not include this milestone | ☐ | ☐ | ☐ |
| Meeting pre-requisites not met (e.g., meeting deliverable incomplete, last minute revisions being made with review) | ☐ | ☐ | ☐ |
| Advisory Committee meeting | ☐ | ☐ | ☐ |
| Other (please specify) | | | |

21) In your opinion, a primary review is considered completed when:

- ☐ The review is drafted by a discipline reviewer, awaiting secondary sign-off and not yet logged into DARRTS or RMS/BLA
- ☐ The review is drafted by a discipline reviewer and received secondary sign-off, but not yet logged into DARRTS or RMS/BLA
- ☐ The review is drafted by a discipline reviewer, received secondary sign-off, and logged into DARRTS or RMS/BLA
- ☐ Other (please specify)

22) Discipline Reviewers Only – In your experience, what factors are the most common barriers to completing the primary review on time? Please mark all that apply.

- ☐ Waiting for input from discipline review
- ☐ Waiting for response from a consult
- ☐ Waiting for response from an inspection
- ☐ Late amendment/response to information request from sponsor
- ☐ Advisory committee meeting
- ☐ Team leader availability to perform review and sign-off
- ☐ Competing workload/priorities
- ☐ Others (please specify)

23) Discipline Reviewers Only – If you chose "competing workload/priorities" as a factor in the previous question, how frequently do the following specific elements of work interfere with timely completion of primary reviews?

| | Very frequently | Somewhat frequently | Somewhat rarely | Very rarely |
|---|---|---|---|---|
| Other NDA/BLA review | ☐ | ☐ | ☐ | ☐ |
| IND review | ☐ | ☐ | ☐ | ☐ |
| SPA review | ☐ | ☐ | ☐ | ☐ |
| Unanticipated special projects | ☐ | ☐ | ☐ | ☐ |
| Committee work | ☐ | ☐ | ☐ | ☐ |

Please provide any additional comments about this question.

24) How likely do you believe it is that GRMPs compliance for the milestone "Completing Primary Review" would improve if separate internal milestones were set for each review discipline to coordinate primary review completion timelines (e.g., discipline reviews that were important to inform other discipline reviews were completed slightly earlier)?

☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

Please provide any additional comments you have about this question.

25) Discipline Reviewers Only – On which other discipline reviews are you typically dependent to complete your review? Please check all that apply.

- ☐ Clinical
- ☐ Non-Clinical
- ☐ Clinical Pharmacology
- ☐ Biostatistics
- ☐ Product Quality
- ☐ My review is generally not dependent on other discipline reviews

## Action Phase

26) How likely do you believe it is that setting a milestone date to complete final labeling would increase compliance with final pre-action GRMPs milestone steps (i.e., compiling action package, circulating action package and letter for review, signatory authority sign-off)?

☐ Very Likely ☐ Somewhat Likely ☐ Somewhat Unlikely ☐ Very Unlikely

Please provide any additional comments you have about this question.

27) How frequently do each of the following factors explain the initiation of labeling review and discussions with sponsors after the GRMPs-specified timeframe?

| | Very frequently | Somewhat frequently | Somewhat rarely | Very rarely | Never |
|---|---|---|---|---|---|
| Late labeling submissions from sponsors | ☐ | ☐ | ☐ | ☐ | ☐ |
| Late completion of primary reviews | ☐ | ☐ | ☐ | ☐ | ☐ |
| Expectation of a Complete Response action | ☐ | ☐ | ☐ | ☐ | ☐ |
| Not aware of/concerned with this GRMPs milestone | ☐ | ☐ | ☐ | ☐ | ☐ |

Please provide any additional comments about this question.

28) RPMs Only – In your experience, what are the most frequent reasons why final pre-action steps are not done by the GRMPs-specified timeframe (e.g., compiling action package, circulating action package and letter for review, signatory authority sign-off)?

| | Very frequently | Somewhat frequently | Somewhat rarely | Very rarely |
|---|---|---|---|---|
| Late completion of primary review | ☐ | ☐ | ☐ | ☐ |
| Late completion of labeling | ☐ | ☐ | ☐ | ☐ |
| Late completion of REMS | ☐ | ☐ | ☐ | ☐ |
| Late completion of PMR/PMCs | ☐ | ☐ | ☐ | ☐ |
| GRMPs lead time for action package/letter review is not necessary | ☐ | ☐ | ☐ | ☐ |
| Not aware of/concerned with this GRMPs milestone date | ☐ | ☐ | ☐ | ☐ |
| Competing workload/priorities | ☐ | ☐ | ☐ | ☐ |

Please provide any additional comments about this question.

29) How much time do you believe is needed to give the signatory authority to thoroughly review the action package before signing off (i.e., lead time prior to PDUFA goal date for RPM to deliver action package/letter to signatory authority)?

- 2 days or less
- 1 week or less
- 2 weeks or less
- 3 weeks or less
- More than 3 weeks

Please provide any additional comments you have about this question.

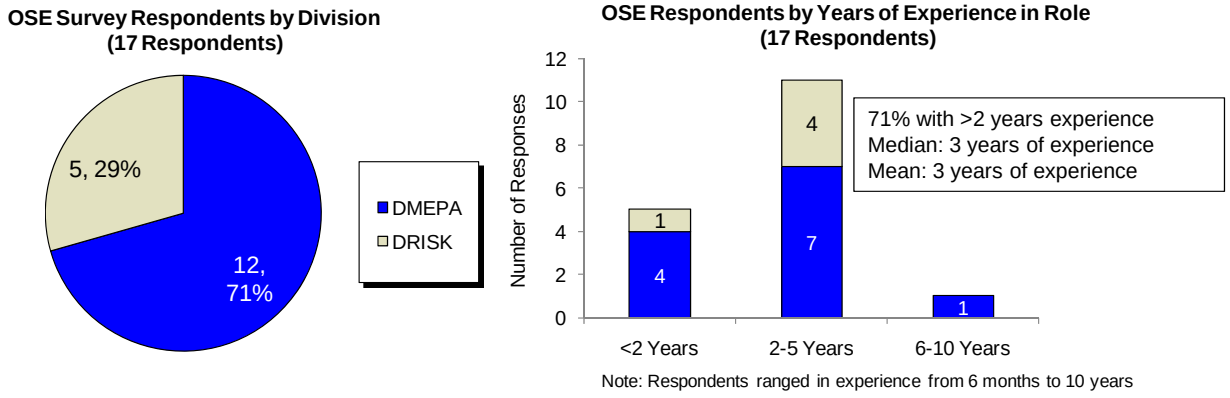
**Recommendations**

30) Are there any tools, training or processes that would help you perform your role in NDA/BLA review and improve GRMPs compliance?

31) Please provide any other suggestions or comments to improve implementation of the GRMPs.

## E.2 Office of Surveillance and Epidemiology (OSE) Respondent Characteristics and Survey Questions

**Exhibit 53. Respondent Characteristics for FDA Office of Surveillance and Epidemiology (OSE) Survey**




**Office of Surveillance and Epidemiology Survey**

1) In which Division do you currently work?

- DMEPA
- DRISK

2) How many years have you worked in this role at the FDA?

3) How frequently do you attend each of the following major milestone meetings?

| | Very frequently | Somewhat frequently | Somewhat rarely | Very rarely |
|---|---|---|---|---|
| Filing/Planning Meeting | ☐ | ☐ | ☐ | ☐ |
| Mid-Cycle Meeting | ☐ | ☐ | ☐ | ☐ |
| Wrap-Up Meeting | ☐ | ☐ | ☐ | ☐ |

Please provide any additional comments about this question.

4) If you answered that you attend the FILING/PLANNING meeting "Somewhat Rarely" or "Very Rarely", what are the most common reasons for not attending more regularly?
- ☐ Not informed of/not invited to meeting
- ☐ Not required to attend
- ☐ Do not perceive attendance would be useful
- ☐ Competing workload
- ☐ Scheduling conflict
- ☐ Other (please specify)

5) If you answered that you attend the MID-CYCLE meeting "Somewhat Rarely" or "Very Rarely", what are the most common reasons for not attending more regularly?
- ☐ Not informed of/not invited to meeting
- ☐ Not required to attend
- ☐ Do not perceive attendance would be useful
- ☐ Competing workload
- ☐ Scheduling conflict
- ☐ Other (please specify)

6) If you answered that you attend the WRAP-UP meeting "Somewhat Rarely" or "Very Rarely", what are the most common reasons for not attending more regularly?
- ☐ Not informed of/not invited to meeting
- ☐ Not required to attend
- ☐ Do not perceive attendance would be useful
- ☐ Competing workload
- ☐ Scheduling conflict
- ☐ Other (please specify)

7) When are you typically asked to complete the labeling review?
- ☐ By mid-cycle meeting
- ☐ By wrap-up meeting
- ☐ By PDUFA goal date
- ☐ Usually not provided with a specific timeframe for completion
- ☐ Not applicable to my role
- ☐ Other (please specify)

8) In your experience, what are the main challenges in completing the labeling review within GRMPs timeframes? (answer only if applicable)

9) Are there any consequences for you or your division/office for not completing labeling review by the timeframe requested?
- ☐ Yes ☐ No

10) In your experience, what are the main challenges in completing development of PMRs/PMCs within GRMPs timeframes? (answer only if applicable)

11) Are there any consequences for you or your division/office for not completing PMR/PMC development by the timeframe requested?

☐ Yes ☐ No

Please provide any additional comments about this question.

12) In your experience, what are the main challenges in completing development of REMS within GRMPs timeframes? (answer only if applicable)

13) Are there any consequences for you or your division/office for not completing REMS development by the timeframe requested?

☐ Yes ☐ No

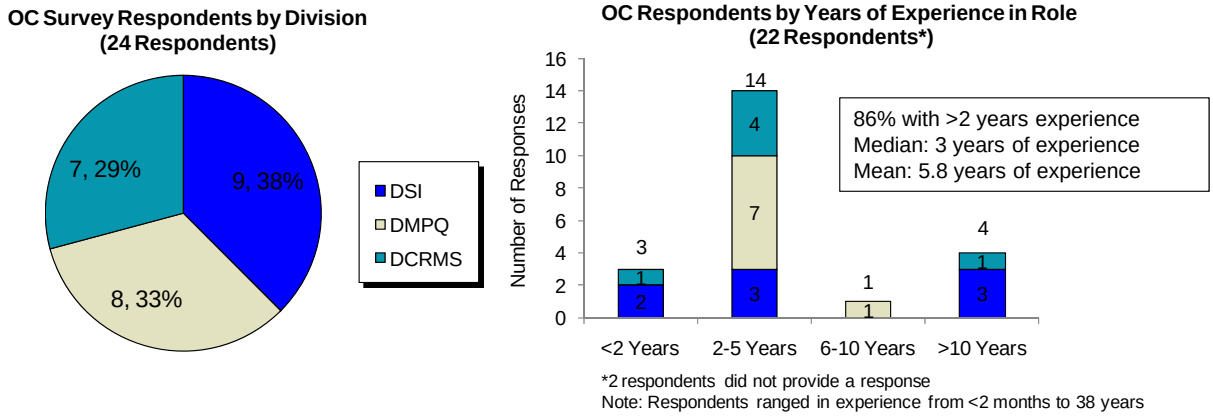
Please provide any additional comments about this question.

14) Are there any improvements to the current review process that would better enable you to help the review team meet GRMPs milestones?

15) Please provide any additional comments you have about your role and experience with the GRMPs that have not been covered in the survey.

## E.3 Office of Compliance (OC) Respondent Characteristics and Survey Questions

**Exhibit 54. Respondent Characteristics for FDA Office of Compliance (OC) Survey**




### Office of Compliance Survey

1) In which Division do you currently work?

☐ DSI
☐ DMPQ
☐ DCRMS

2) How many years have you worked in this role at the FDA?

3) How frequently do you attend each of the following major milestone meetings?

| | Very frequently | Somewhat frequently | Somewhat rarely | Very rarely |
|---|---|---|---|---|
| Filing/Planning Meeting | ☐ | ☐ | ☐ | ☐ |
| Mid-Cycle Meeting | ☐ | ☐ | ☐ | ☐ |
| Wrap-Up Meeting | ☐ | ☐ | ☐ | ☐ |

Please provide any additional comments about this question.

4) If you answered that you attend the FILING/PLANNING meeting "Somewhat Rarely" or "Very Rarely", what are the most common reasons for not attending more regularly?

- ☐ Not informed of/not invited to meeting
- ☐ Not required to attend
- ☐ Do not perceive attendance would be useful
- ☐ Competing workload
- ☐ Scheduling conflict
- ☐ Other (please specify)

5) If you answered that you attend the MID-CYCLE meeting "Somewhat Rarely" or "Very Rarely", what are the most common reasons for not attending more regularly?

- ☐ Not informed of/not invited to meeting
- ☐ Not required to attend
- ☐ Do not perceive attendance would be useful
- ☐ Competing workload
- ☐ Scheduling conflict
- ☐ Other (please specify)

6) If you answered that you attend the WRAP-UP meeting "Somewhat Rarely" or "Very Rarely", what are the most common reasons for not attending more regularly?

- ☐ Not informed of/not invited to meeting
- ☐ Not required to attend
- ☐ Do not perceive attendance would be useful
- ☐ Competing workload
- ☐ Scheduling conflict
- ☐ Other (please specify)

7) Is there sufficient time in the current process to conduct/coordinate inspections?

- ☐ Yes
- ☐ No

Please provide any additional comments you have on this question.

8) When there is not sufficient time to coordinate/complete inspections, what are the most common reasons?

- ☐ Foreign inspection site
- ☐ Late determination/notification of needed inspection
- ☐ Competing workload
- ☐ Other (please specify)

9) Are there any consequences for you or your division/office for not completing inspections by the timeframe requested?

- ☐ Yes
- ☐ No

Please provide any additional comments about this question.

10) In your experience, what are the main challenges in completing development of PMRs/PMCs within GRMPs timeframes? (answer only if applicable)

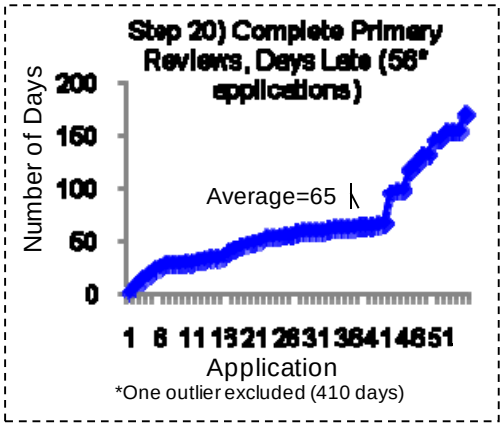
11) In your experience, what are the main challenges in completing development of REMS within GRMPs timeframes? (answer only if applicable)

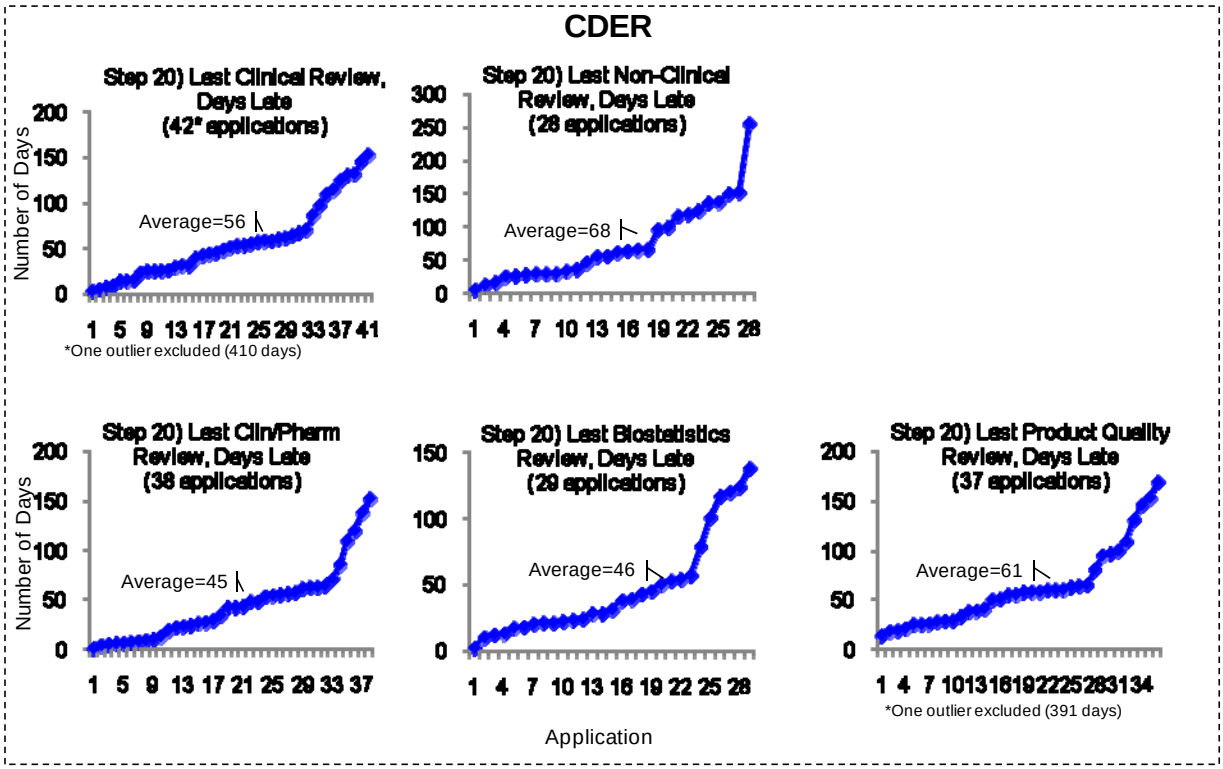
12) Are there any improvements to the current review process that would better enable you to help the review team meet GRMPs milestones?

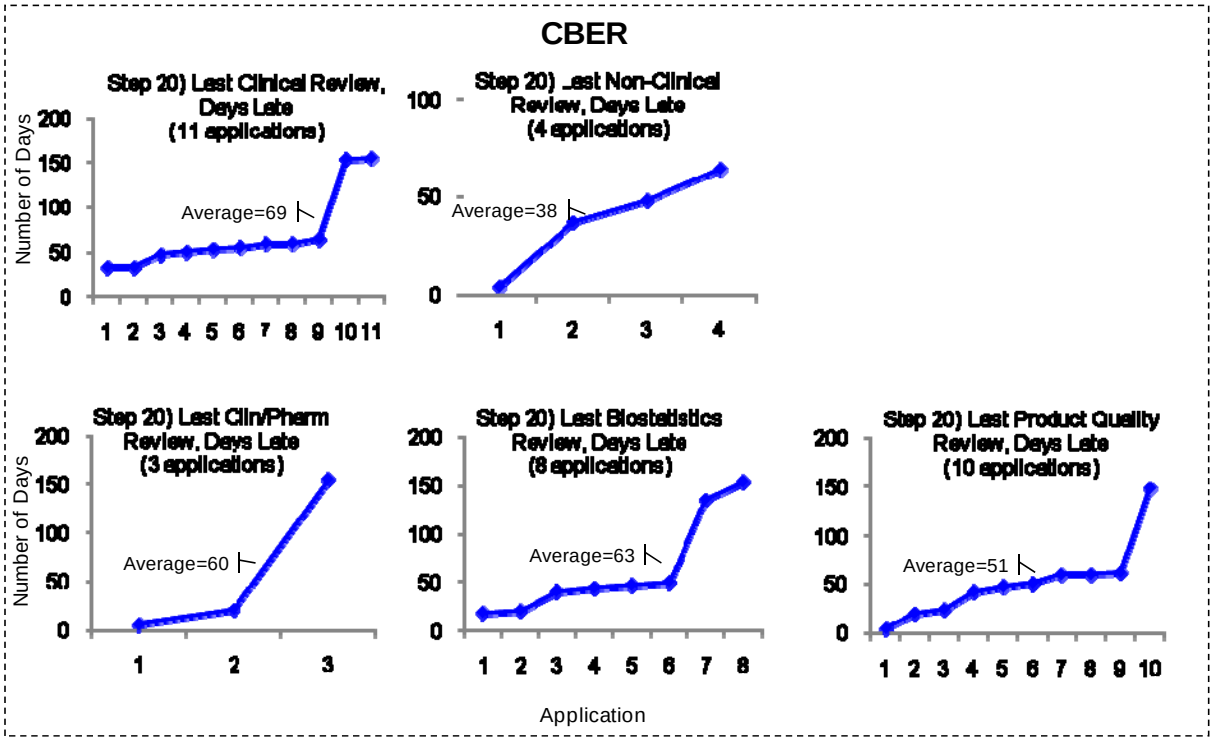
13) Please provide any additional comments you have about your role and experience with the GRMPs that have not been covered in the survey.

# Appendix F: Distribution Curves by Discipline for Late Completion of Primary Reviews

Primary discipline reviews were not completed on time for 92% of cohort applications. For these applications, distribution curves below display the average number of days late that reviews were completed across Centers, as well as the average number of days late that reviews were completed for each review discipline in CDER and CBER.




CBER
Step 20) Last Clinical Review, Days Late (11 applications)
Average=69
Step 20) Last Non-Clinical Review, Days Late (4 applications)
Average=38
Step 20) Last Clin/Pharm Review, Days Late (3 applications)
Average=60
Step 20) Last Biostatistics Review, Days Late (8 applications)
Average=63
Step 20) Last Product Quality Review, Days Late (10 applications)
Average=51
Number of Days
Application