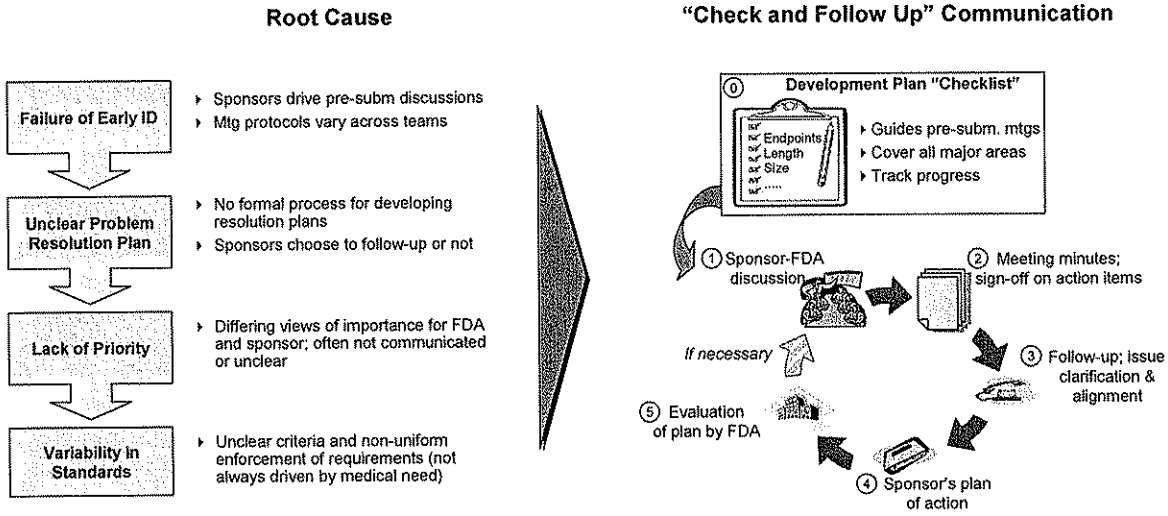
EXHIBIT 4
(Part 2 of 2)

Communication Style and Timing

A root cause of problems in issue identification and resolution can be traced directly to the effectiveness and timing of communication between sponsors and the FDA. Currently, sponsors are responsible for requesting pre-submission meetings to discuss specific issues. While the FDA can also raise questions at these meetings, most divisions do not have formal protocols in place to ensure all key areas are covered. Further, in divisions where protocols do exist, they are not always applied consistently. As a result, issues may not be prioritized and follow up is solely at the sponsor's discretion. Finally, there is no consistent standard for issue resolution across divisions, and adoption of FDA suggestions and requirements prior to submission varies broadly.

An open and accountable communication system centered around issue resolution may increase consistency and transparency in issue identification as well as resolution (Exhibit 20). This system – termed in this report as check-and-follow up communication – may include checklists generated by each division will guide discussions between the sponsor and the FDA and help track sponsor progress against key drug development issues and requirements. Formal follow-up mechanisms in the form of meeting minutes and teleconferences, with appropriate sign-off, will serve to clarify and align the FDA and the sponsor's understanding of the key issues. Sponsor-submitted plans of action proposing approaches to issues raised are reviewed by the FDA to gain agreement on necessary measures for resolution. Such a system will reduce the potential for key issues being overlooked or neglected, and reduce the risk of unforeseen complications arising late in the review process. All divisions interviewed agreed that creation of a checklist with sufficient customization to meet the needs of each therapeutic area is feasible.

Exhibit 20. Check-and-Follow Up Communication



This enhanced FDA-Sponsor interaction tool can be deployed at the earliest stages, beginning with the pre-IND phase (Exhibit 21). These meetings represent an early opportunity to ground the FDA and sponsors on the key issues by informing the FDA of the sponsor's strategy and development plan, and providing the opportunity for feedback where appropriate. Progress can be tracked and future plans and protocols developed at EOP2 meetings. A mid-Phase 3 meeting provides an opportunity to review progress against development plans and design

course corrections, if necessary. Finally, in addition to the discussions of submission protocol and format, trial results and data quality can be assessed prior to filing at the pre-NDA/BLA meetings.

Full realization of the benefits of this communication system will require participation and commitment of both the FDA and sponsors to engage in open discussions and follow through by executing problem resolution plans in a timely manner before applications are submitted.

In light of resource constraints, the FDA may consider a phased implementation approach, initially focusing on developing the checklists. This may already yield sufficient improvements diminishing the urgency for implementing the feedback loop. A pilot program will yield a clearer understanding of the costs, resource requirements and benefits.

Exhibit 21. FDA-Sponsor Interaction Opportunities

Meeting	Objective	Comments
Pre-IND	**Discuss Product Strategy**	Understand sponsor's strategy and product development plan; provide feedback, if appropriate —"everybody on the same page"
	Early Regulatory Input	Rudimentary labeling discussions enable the FDA to provide input on appropriateness of studies
EOP2	**Track Progress**	Discuss progress against development hurdles (e.g., checklist)
	Develop Future Plans	Phase 3 protocol development, approval criteria, follow-up with Special Protocol Assessment (SPA)
Mid-Phase III	**Discuss Challenges**	Review data and discuss deviations from original plan; discuss implementation issues, and major protocol violations
	Refine Studies	Course corrections, as necessary; track progress against development hurdles
Pre-NDA/BLA	**Discuss Data**	Broad overview of trial results, assessment data quality and completeness
	Submission Criteria	Clarify format, discuss inspection status, gain FDA opinion on application "readiness"

Broad variations exist for assessing overall progress during the review period. Of the possible formal meetings held during this period, only the sponsor presentation offers an opportunity for interaction between the FDA and sponsors prior to first action. However, few divisions routinely take advantage of this opportunity (Exhibit 22).

Exhibit 22. FDA Meeting Routine by Division

Meeting Routine During Review by Division

Division	1st Team Mtg	Sponsor Pres.	Filing Meeting	Mid-Cycle	Post Action
A	●	○	●	●	○
B	◑	◑	●	○	◑
C	○	◑	●	●	○
D	○	○	●	◑	◑
E	◑	◑	●	◑	◑
F	●	○	●	●	○
G	◑	○	●	○	○
H	○	○	●	○	◑

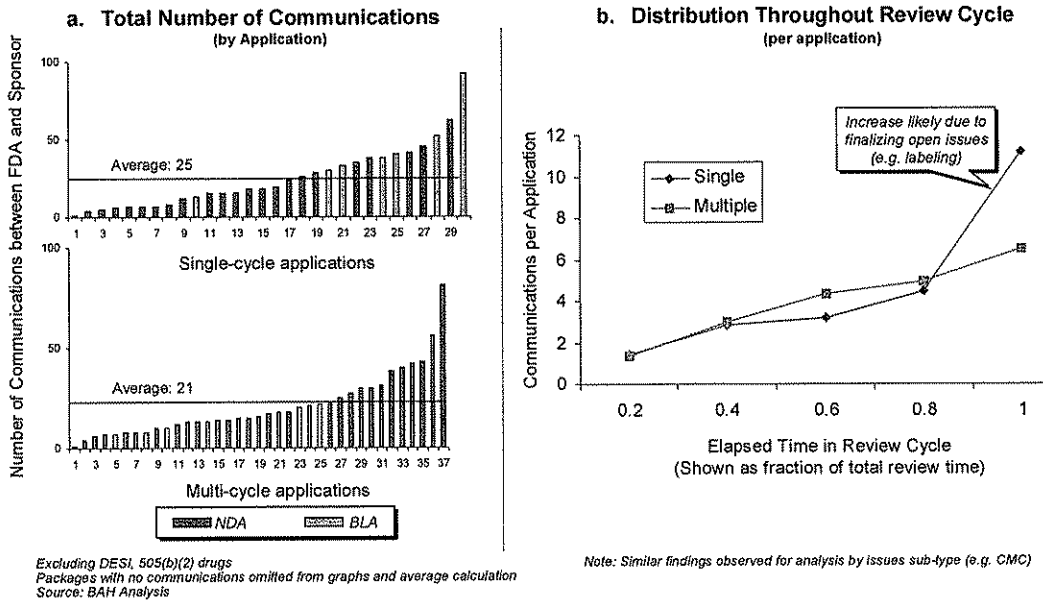
Legend:
1st Team Mtg – Internal planning mtg. w/in 45 days of submission
Sponsor Presentation – Within 45 days of submission
Filing Mtg – Establish suitability of application for filing
Mid-Cycle – Mid-Cycle meeting with review team
Post Action – Discuss "lessons learned" or clarification of deficiencies with sponsor

● Frequently ◑ Occasionally ○ Rarely

Source: Division Interviews

The FDA and sponsors frequently engage in less formal communications, for example email or telephone requests for information. Analysis of action packages revealed that broad variation existed in both the frequency of such communications (Exhibit 23a) or their distribution throughout the review (Exhibit 23b). As can be observed however, there was no systemic difference with respect to these parameters and the number of review cycles required for approval. A slight increase in communications was seen towards the end of reviews for single cycle approval compared to multiple cycle applications. This increase is likely attributable to final resolution of minor issues and labeling discussions.

Exhibit 23. FDA-Sponsor Communications

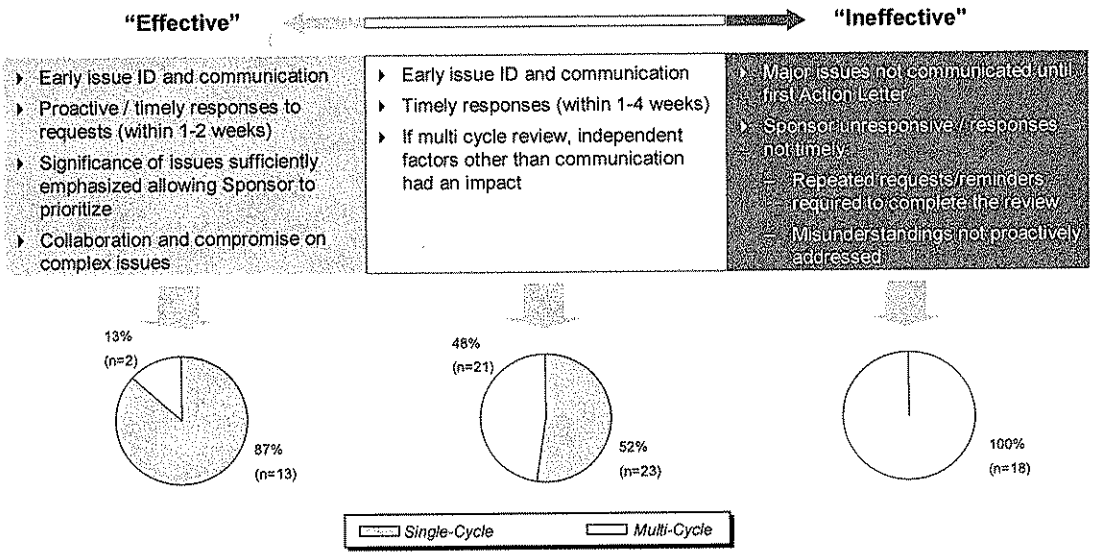


Excluding DESI, 505(b)(2) drugs
Packages with no communications omitted from graphs and average calculation
Source: BAH Analysis

Note: Similar findings observed for analysis by issues sub-type (e.g. CMC)

The tone of most FDA-sponsor communications is positive in nature and does not appear to be a significant driver of single vs. multiple cycle reviews. However, at its extremes, communication styles can impact the review outcome. Effective communication and responsiveness – characterized by early identification and communication of issues and timely responses to requests for information (typically within one to two weeks) – contribute to favorable first-cycle outcomes (Exhibit 24). Communications labeled "ineffective", on the other hand, are characterized by late communication of issues and lack of responsiveness by sponsors. In some cases, key issues were not conveyed to the sponsor prior to the action letter. Conversely, repeated requests for information from the FDA were necessary before sponsor responses were received. All products falling in this category failed to obtain approval in the first review cycle.

Exhibit 24. Effect of Communication Style on First-Cycle Approval Rate



Note: Not all characteristics apply to each application within the category
Source: BAH Analysis

In some product reviews, disagreements and/or sustained misunderstandings prevented the FDA and sponsors from resolving outstanding issues and ultimately led to the need for additional review cycles before the product could be approved (Exhibit 25).

Exhibit 25. Multi-Cycle Product Reviews Marked with Ineffective FDA-Sponsor Interaction

Product M	Consistent misunderstanding of FDA requests may have prolonged review and contributed to a second cycle
Product N	Disagreements over schedule IV classification impacted outcome; formal dispute resolution was required
Product O	Consistent misunderstanding between the FDA and sponsor impacted the ability to reach timely agreements
Product P	Sponsor insisted on not following FDA advice regarding trial design; data quality was marginal with frequent clarifications necessary

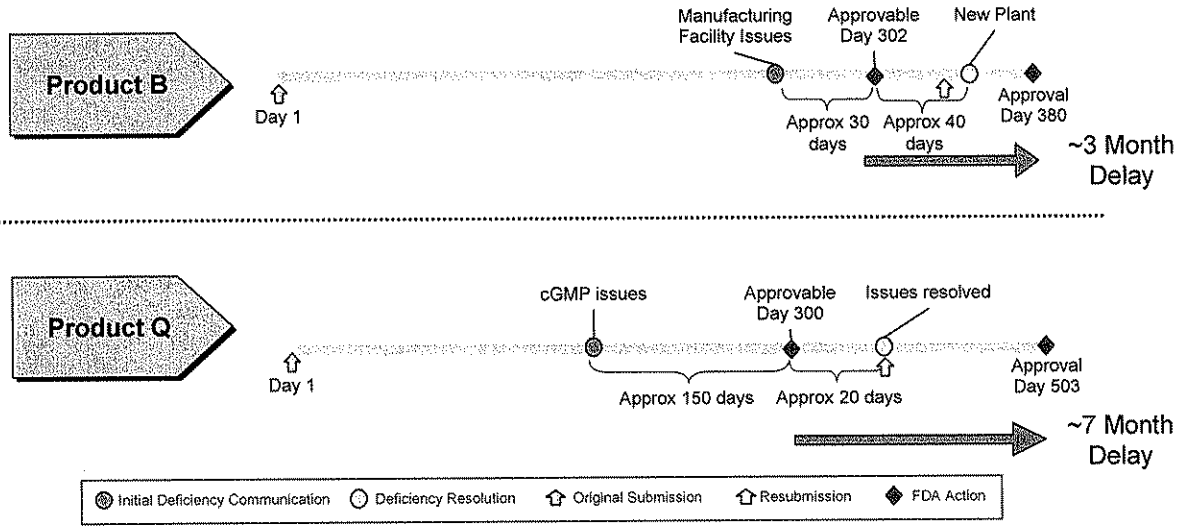
In addition, there are examples where earlier communication of key issues within the review cycle may have led to resolution in time to gain first-cycle approval. **Error! Reference source not found.** depicts two cases where the relative short period of time required for resolution of the key issues preventing approval may have been readily accommodated within the first review cycle, had the issues been identified and communicated to the sponsor only three to four weeks earlier. The underlying assumption is that earlier identification would have been feasible, and that the FDA would have sufficient time within the first review cycle to review resubmissions:

> Product B: An unacceptable manufacturing plant and missing packaging/stability data were the key issues cited in the first action letter. These were initially

communicated to the sponsor shortly before the action date. The sponsor provided a compliant facility and missing data were submitted approximately one month after the action date

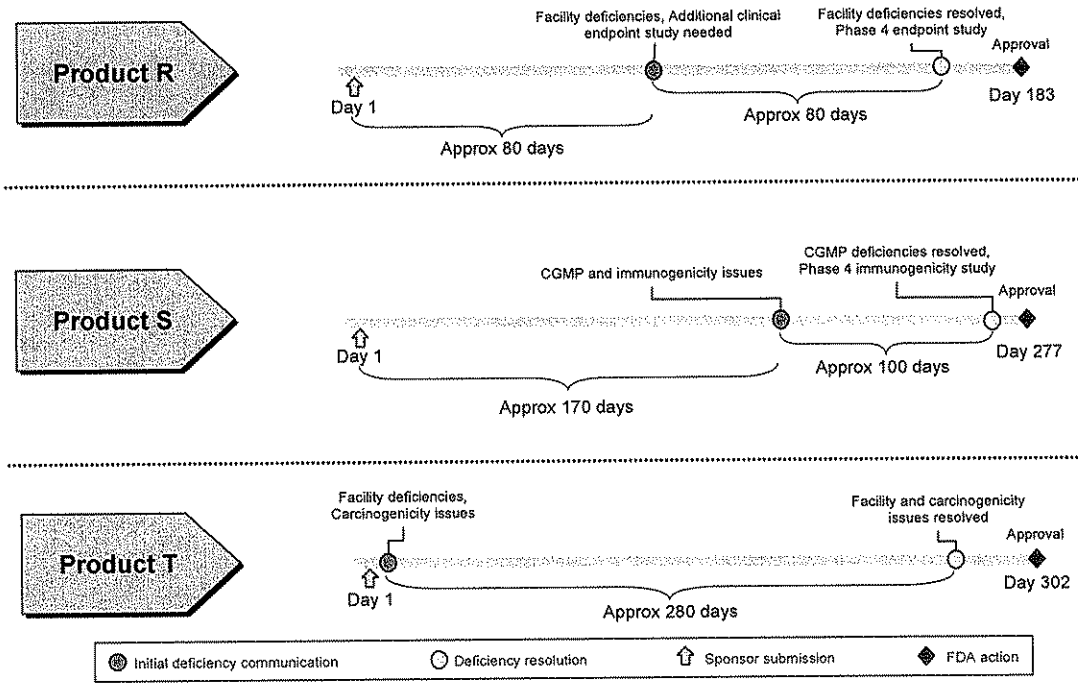
- Product Q: CMC deficiencies represented 95% of issues listed in the first action letter. The sponsor corrected deficiencies and resubmitted the application approximately 20 days after the first action

Exhibit 26. Issue Resolution Timing – Multiple Cycle Applications



Examples of successful issue resolution through effective sponsor-FDA interaction and responsiveness are seen in single cycle applications (Exhibit 27). The examples provided in **Error! Reference source not found.** and Exhibit 27 revolve around CMC deficiencies, suggesting that this discipline may benefit most from earlier communication.

Exhibit 27. Issue Resolution Timing – Single Cycle Applications



Formalized review team communications recommended in the recently introduced GRMP guidance (e.g. Filing, Mid-Cycle meetings) are intended to enforce early engagement of review teams and increase the dialog with sponsors. Exhibit 28 lists opportunities whereby FDA review teams or FDA and sponsors may come together to facilitate the review process. Supplemented with the additional GRMP-recommended meetings and open dialog, the combined formal and informal meetings may promote more productive communications that span the breadth of the review:

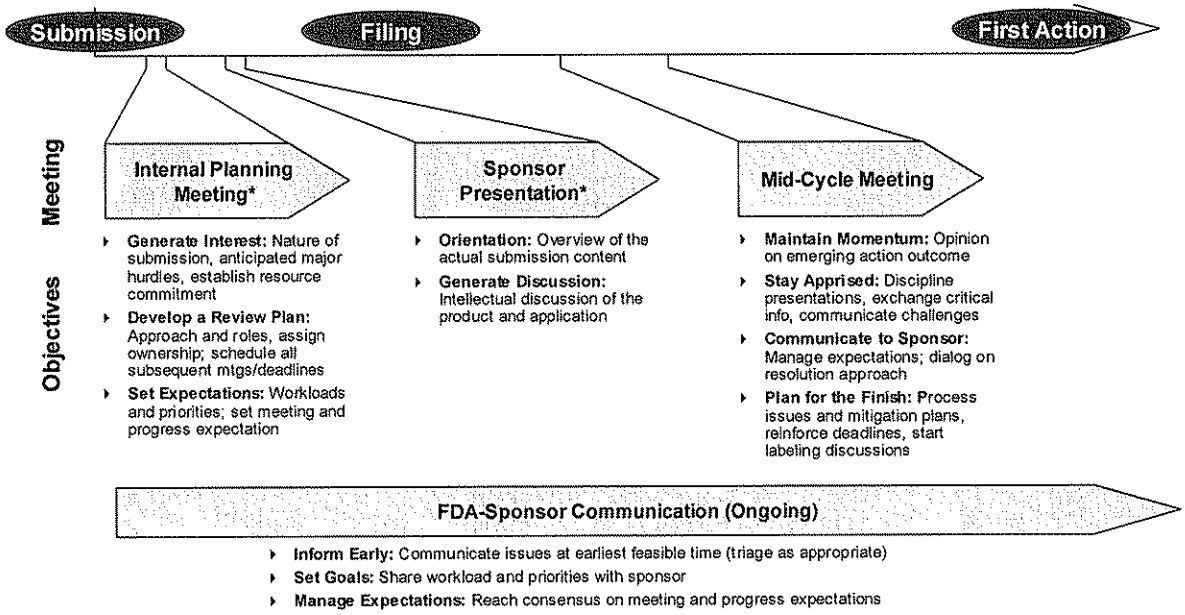
- Internal planning meetings – most effective when held before the filing meeting – create an opportunity to develop review plans and set expectations early in the review process
- Sponsor presentations to the review team – currently rare – can serve to orient reviewers to the actual submission (as opposed to the pre-submission outline), and generate discussion around the product
- Internal meetings – e.g., at the Mid-Cycle stage – offer an opportunity to develop initial, holistic opinions on the emerging outcome and discuss open issues
- Ongoing, proactive dialog with sponsors will ensure that goals are communicated and expectations managed.

A Mid-Cycle meeting can further provide an opportunity to assess whether appropriate levels of resources are deployed to complete the review in a timely manner, and to what extent additional discussions with the sponsor are warranted. Where feasible, these meetings can trigger early labeling discussions which often require several iterations before being accepted by both parties.

The introduction of additional meetings and/or restructuring of existing meetings may have resource implications for the FDA. As previously mentioned, savings from reduced multi-cycle

reviews may however, off-set increased resource demands. Additional resources may be necessary during the period of overlap of current reviews and review of future submissions using the new recommendations.

Exhibit 28. Review Communication Summary



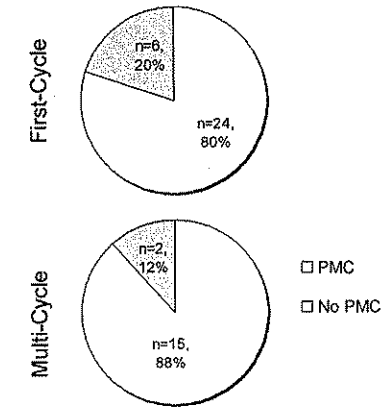
(*): Most beneficial when conducted before the Filing Meeting

Post-Marketing Commitments

Post-marketing commitments (PMCs) provide a mechanism to bring drugs to market more quickly by resolving issues that are not critical for approval during the marketing phase of the product life-cycle. For the cohort products, 80% of single-cycle and 88% of multi-cycle applications were approved with PMCs (Exhibit 29a). The number of PMC requests per application varied broadly, ranging from 2 to 20, with a similar average number of commitments regardless of review cycles (5.4 and 4.4 commitments for single and multiple cycle approvals, respectively, Exhibit 29b). Further, the focus and burden of post-marketing commitments do not differ between first- and multi-cycle approvals, with the majority consisting of additional clinical studies to further evaluate very specific safety and/or efficacy questions (
Exhibit 30).

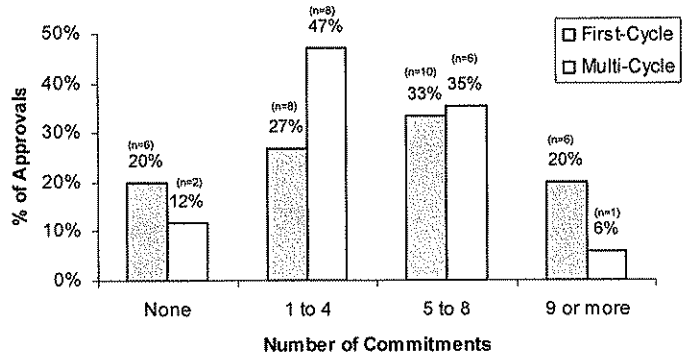
Exhibit 29. Post-Marketing Commitments Single vs. Multi-Cycle Reviews

a. % of Approved Drugs with Post-Marketing Commitments by Cycle



Note: Not including DESI, 505(b)(2) drugs

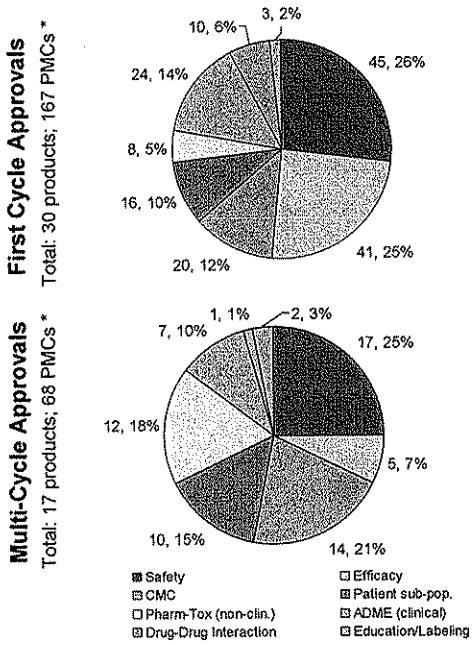
b. Approvals w/ Post-Marketing Commitments by Number of Commitments



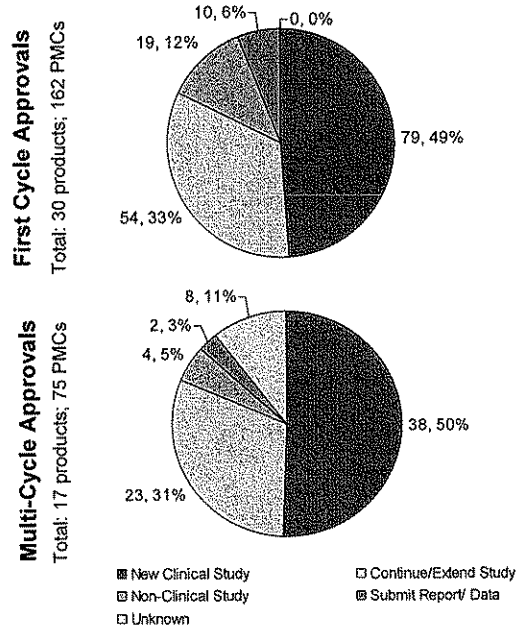
Average per Approval	First-Cycle : 5.4 Multi-Cycle : 4.4

Exhibit 30. Focus and Burden of Post-Marketing Commitments

a. Commitments by Area of Focus



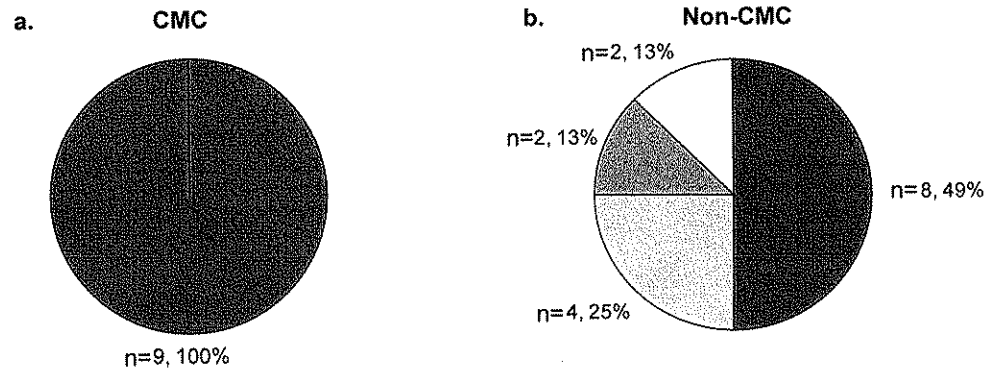
b. Type of Post Marketing Commitment



(1) Includes post-marketing commitments from 39 submissions
(2) Does not include DESI, 505(b)(2) products
(*): Studies to demonstrate safety and efficacy are counted as two areas of focus

A closer inspection of multi-cycle applications revealed that only CMC deficiencies are generally resolved through sponsor compliance of FDA recommendations (Exhibit 31a). Of the critical, non-CMC related issues, approximately 50% are resolved by complying with FDA requests. The remaining issues are resolved through an agreement to perform PMCs or via an alternative path (Exhibit 31b), based on additional discussions between sponsors and the FDA.

Exhibit 31. Disposition of Significant First Action Deficiencies in Multi-Cycle Approvals



Analysis includes 18 multi cycle approved products, some had >1 major issue
Source: BAH Analysis

In two instances of products receiving approval after the second review cycle, the key deficiency preventing first cycle approval could not be fully resolved, and disagreements persisted:

- Product U: Unknown consequences of a chemical element accumulation, prompted the FDA to request additional studies. New data did not provide adequate resolution of the safety issue. Approval after second review required a PMC to assess the effects of long-term the chemical element accumulation
- Product V: Concern over the design of a safety study prevented first cycle approval. Interpretation of new study data remained inconclusive and depended on how the data was analyzed. The Office Director after further review and analysis approved the product with no Phase 4 commitment request related to the safety issue.

Interviews confirmed that divisions generally do not have consensus on PMC policy before communicating with sponsors. This has resulted in inconsistent usage between divisions or within divisions for different products, and some divisions largely avoid PMCs altogether due to difficulties in enforcement. Promoting earlier discussions between the FDA and sponsors and providing clearer guidelines on alternative acceptable pathways for addressing deficiencies will allow sponsors to focus efforts on the key requirements for approval, while shifting less critical issues to the post-market phase. This may reduce the time to market; in some cases through approval within the first review cycle.

Guidance for the use of PMCs is necessary to provide transparency and facilitate negotiations with sponsors. An understanding of division PMC practices/philosophies will help formulate PMC policies. Sponsors will benefit from the ability to prioritize deficiencies based on a clear understanding of issues that can be addressed through to PMCs versus ones that have to be resolved prior to approval. An approach to developing such guidances should involve establishing standardized principles across divisions and incorporating best practices for monitoring and revising labels as results from these studies emerge. Customization to the individual therapeutic areas and disciplines is necessary to ensure the effectiveness of these guidances. Interviewees agreed that creation of such guidances with a meaningful level of customization would be feasible.

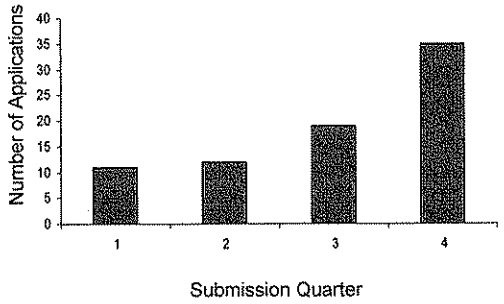
FDA Characteristics

FDA Workload

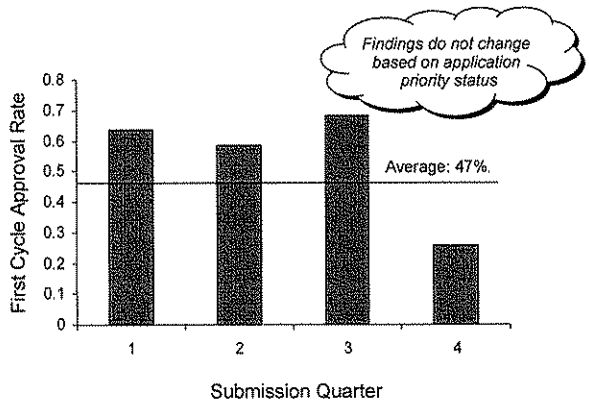
Between two and three times as many applications are submitted in the fourth quarter of each calendar year than any other quarter (Exhibit 32a), with Q4 applications having a 26% 1st-cycle approval rate versus 64% for Q1-Q3 submissions (Exhibit 32b).

Exhibit 32. Submission Timing vs. Number of Submissions or First-Cycle Approval Rates

a. Number of Submissions by Quarter (aggregate 2001-2004*)



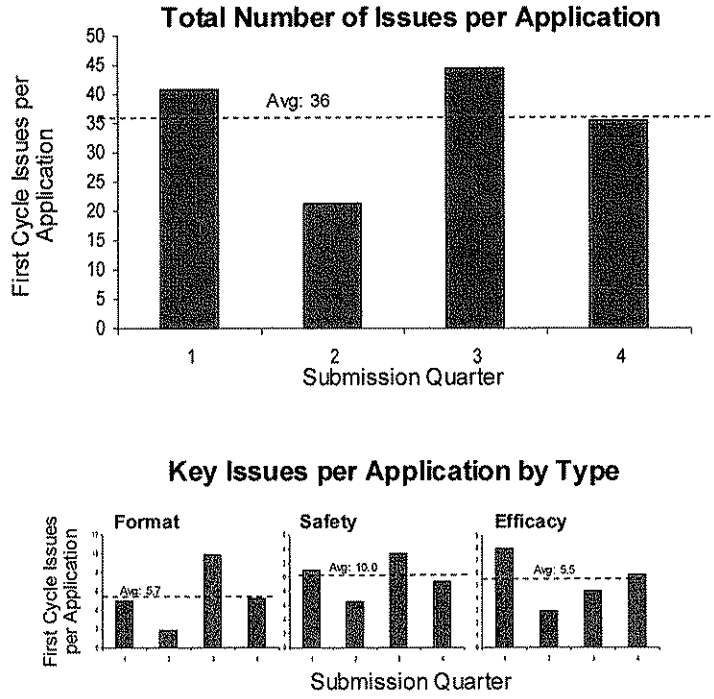
b. Approval Rate by Quarter Submitted



(*): Similar findings observed for individual years

FDA interviewees attributed this finding to their perception that Q4 applications are often of lower quality, requiring greater review effort and failing to meet approval criteria. However, this could not be verified in this study, as Q4 submissions had similar numbers of issues compared to other quarter submissions when measured by the total number of issues communicated or the issue category (i.e. safety, efficiency, format. see Exhibit 33). This points to potential FDA staff workload issues, with all PDUFA goal dates coinciding around a similar timeframe. Furthermore, workload issues may be compounded by the coincidence of the end of review cycles with the generally lower staffing during the summer months. Further analysis is necessary to understand the nature of the application issues for better comparison of application quality and workload.

Exhibit 33. Submission Timing vs. Number or Type of Issues per Application



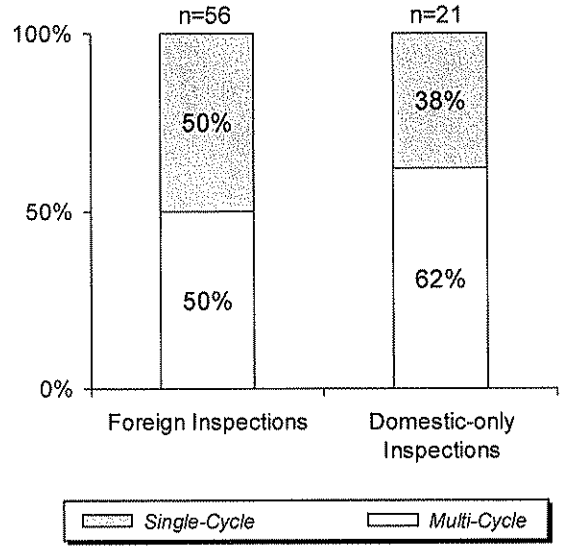
Sources: BAH Analysis; Division Interviews

GMP Inspection Process

Clinical protocol and Current Good Manufacturing Practice (CGMP) compliance are integral to the review process and action. For an efficient review, FDA reviewers stressed the importance of effective internal communication with divisions overseeing manufacturing compliance. Interviewees cited that delays in CGMP inspections can slow the review process and/or result in multi-cycle reviews. In the cohort analyzed, 10 of 18 (56%) multi-cycle applications that were approved in two or more cycles had inspection deficiencies listed in the first-cycle action letter. Manufacturing deficiencies uncovered late in the review cycle may not allow sponsors sufficient time to correct issues before the goal date. This concern was particularly pronounced for applications requiring inspections at foreign locations which, due to increased administrative requirements as well as field inspector resource constraints, generally have longer lead times.

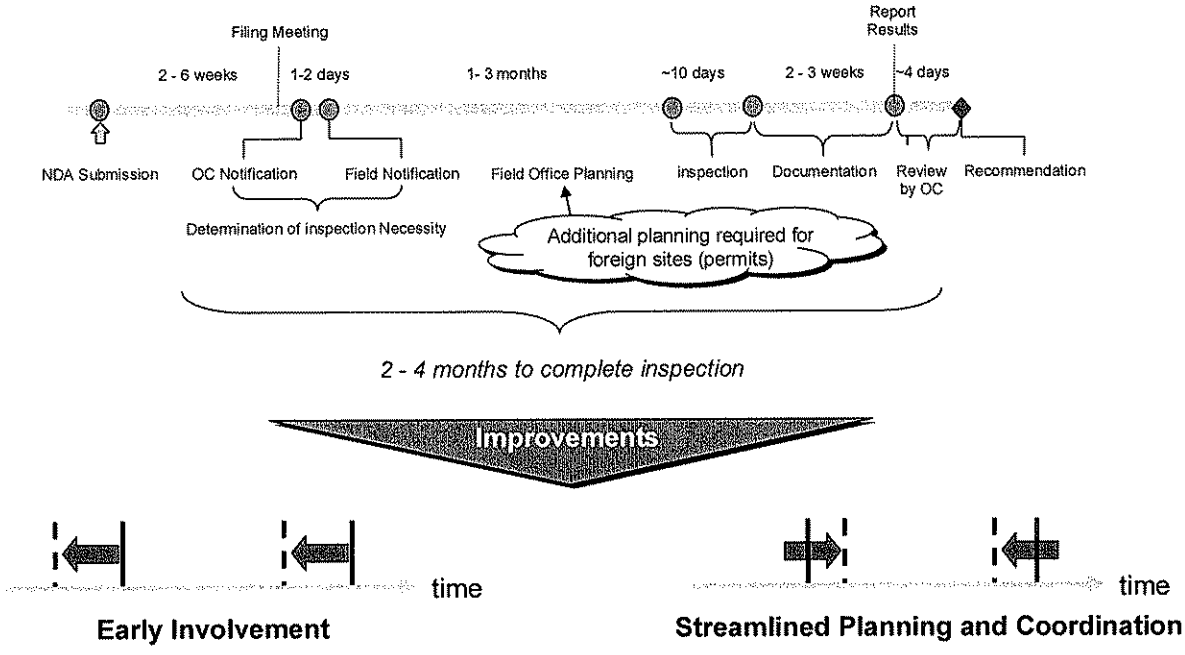
A correlation between foreign inspection and multi-cycle approval was not reflected in the analysis, as shown in Exhibit 34. Applications requiring foreign inspections actually had a slightly higher first-cycle approval rate as compared to applications requiring only domestic inspections.

Exhibit 34. Foreign or Domestic CGMP Inspection vs. % of Single or Multiple Review Cycles



Nevertheless, the long lead times for the planning and execution of site inspections (up to four months, with additional vulnerabilities for foreign inspections; see Exhibit 35 for overview of the manufacturing inspection process and representative timelines) can place single cycle approvals at risk, especially for applications with Priority status which have compressed review times. Applications that change status (e.g., from Standard to Priority), or for which additional inspection sites are identified late in the review, are also at added risk.

Exhibit 35. Schematic of the CGMP Inspection Process and Improvement Opportunities

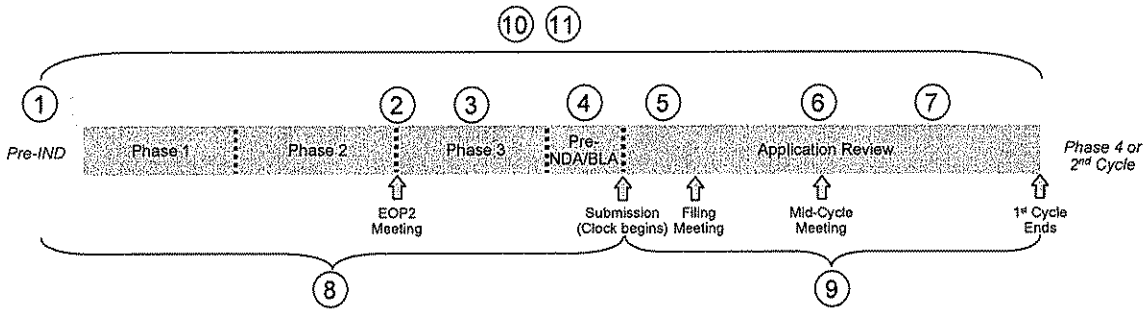


Earlier involvement of Consumer Safety Officers (before or during pre-NDA/BLA meetings) and efforts to streamline inspection planning and execution will mitigate this risk by increasing the sponsor's ability to resolve issues prior to the end of the first-cycle. Division interviews have suggested that inspection officers attending pre-NDA/BLA meetings gain earlier insight that aids the inspection process. Many divisions also encourage early submission of the CMC section of applications. A review of inspection team notification and scheduling can yield insights into ways whereby the planning can be streamlined and long lead times reduced.

SUMMARY OF RECOMMENDATIONS

Exhibit 36 provides a summary of suggested improvement opportunities identified in the retrospective analysis. Emphasis on implementation should, in particular, be placed on less-experienced sponsors who seem to be at greatest risk for multiple cycle review. Earlier and more effective communication with sponsors, enhanced by a check-and-follow up approach, will maximize the potential to identify and communicate issues and develop a resolution plan in a timely manner. Developing guidelines for, and increasing rigor in, the administration of post-marketing commitments may further increase the effectiveness of PMCs, providing patients earlier access to medicines while enabling select open issues to be effectively and reliably assessed after approval. Some of the proposed measures are part of the GRMP guidelines recently published by the FDA. A planned prospective study will attempt to capture the extent to which these guidelines have been implemented, and the costs and benefits that have been realized.

Exhibit 36. Summary Overview of Recommendations



1. Pre-IND - Product strategy discussion with the sponsor
2. EOP2 – Phase 3 planning, sponsor follow-ups up with SPAs
3. Mid-Phase 3 – Discuss preliminary results
4. Involve OC/DMPQ at pre-NDA/BLA
5. Early review cycle - sponsor presentation and internal planning meeting
6. Mid-Cycle Meeting - Discipline presentations
7. A Division guide for post-marketing commitment development
8. Use checklist to support FDA-sponsor discussions
9. A "check and follow-up" system for issue resolution
10. Inexperienced/Foreign Sponsors hire appropriate outside expertise
11. Guidance and website management

Note: Some Divisions already have some of these concepts in place