Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs

PhRMA

1866 '03 SEP 11 P12:35

September 11, 2003

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0317; Draft Guidance for Reviewers and Industry on Good Review Management Principles for Prescription Drug User Fee Act Products; 68 Federal Register 44345

Dear Sir/Madam:

The following comments on the above noted draft Guidance document regarding Good Review Management Principles (GRMPs) are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over $32 billion in the discovery and development of new medicines.

EXECUTIVE SUMMARY:

- Overall the document needs to be more specific. The use of general terms in the guidance is discouraged. More detail with respect to timing and timelines will result in clear expectations on behalf of the applicant and FDA. Common terminology consistent with current expectations is suggested.

- The document needs to define a more transparent process. Direct dialogue should be encouraged throughout the review process. The discussion on inclusion of amendments in the first review cycle does not allow the applicant to understand the review strategy and timeline. Clear, direct communication will allow both the applicant and FDA to be prepared with appropriate resources. The inclusion of consultants in the review process should be transparent to the applicant. Consultants with authority for final recommendations should be considered adjunct members of the review team and included in presubmission meetings.

- Timing and timelines need to be added to the document. It is common for last-minute discussions to occur regarding labeling language, tradename, immediate container and packaging, post-approval commitments, and risk management plans. Definition of timing for review of tradename, container/packaging and labeling proposals would allow the applicant and FDA to prepare with adequate resources and schedule discussions upfront. If time for communication between the FDA and the applicant on potential post-approval commitments is not planned as part of a well-managed review process, it can result in hasty commitments

2003D-0317 C4

leading to poorly conceived studies that are not feasible to complete, or that are not capable of providing the desired information. Timing for the review of risk management plans also needs to be discussed in the document to avoid delays.

- More detail should be added on the following processes to facilitate good review management principles:
    1. Meetings and agreements – Clearly delineated expectations and recommendations will result in a more efficient review.
    2. Information transfer to review teams – If the review team is different from the team involved in the IND review and presubmission meeting discussions, a formal process for information transfer should take place to ensure that issues are not re-discussed during the application review.
    3. Inspections – Facility inspections are part of the review process and as such should be included in good review management.
    4. Training – Appropriate training is paramount to the success of the initiative.
    5. Lessons learned/wrap-up – A successful process should include metrics beyond timelines. Initiation of a review wrap-up promotes learning and continuous improvement.

GENERAL COMMENTS

1. PhRMA commends the Agency for striving to improve communication and transparency of the review with industry. In an effort to meet this goal, it is suggested that a high-level review timeline with key milestones be shared with the applicant at the beginning of the review process and updated as the timeline is revised. A standard review timeline indicating key review milestones could be included in the guidance. This will facilitate the partnership between the applicant and FDA during the application review by preparing for interactions and responses.

2. Some sections of this document are difficult to interpret. It appears a repeating format is applied to all sections, resulting in repetitive information within a section and throughout the document. It would help to edit the detail and focus the discussion.

3. The draft guidance is often not specific on timelines and often uses words such as "timely" or "as soon as possible". This is not particularly useful in differentiating "good" review management principles. It would be preferable to be more specific, as suggested in the detailed comments on Lines 682 and 1082.

4. The draft guidance includes a number of undefined terms and caveats that undermine the good review principle being described. For example:

   Lines 381 - 383: *"Review team assignments are usually based on the reviewers assigned to the IND for the product. However, in certain cases, new or additional reviewers may be assigned as dictated by workload, competing priorities, application complexity, or review discipline staffing."*

   PhRMA agrees that it is a good review management principle to have the same reviewers assigned to the market application as reviewed the IND. Consideration should also be

given to assign additional reviewers as appropriate. However, if assignment is dictated by workload, competing priorities, application complexity, or staffing problems, it would suggest that at least some assignments do not follow good review management principles but, instead, are forced by external factors.

Lines 442-444: *"A decision regarding the review priority (i.e., priority or standard) for NDAs, BLAs, and efficacy supplements should be made as soon as possible following receipt of the application."*

The phrase "as soon as possible" is unduly vague and should be defined to add clarity to the process. If it is important to initiate or complete the action being described within a short time frame, the guidance ought to specify that time frame, such as "3 working days" or "one week."

5. The document does not explicitly encourage direct reviewer and applicant dialogue to clarify reviewers' questions during the review process. This could be incorporated in Section III.C, *Communication between FDA and Applicant*, in the Overall Principles. GRMP should incorporate such exchanges for greater efficiency.

6. The draft guidance does not provide adequate coverage of the importance of having meetings that have clearly delineated, scientifically sound, and consistent recommendations. Effective meetings can lead to more effective reviews and should be incorporated into the Overall Principles section of this document.

7. The document should strongly encourage earlier communication and participation in application review and in discussion meetings of all staff levels, especially division directors and other potential signatories and/or those responsible for the final approval of the application. This can avoid new issues being raised at the time of final action on an application, thereby avoiding unnecessary "approvable" actions rather than "approval" decisions, which can significantly lengthen the review time.

8. It is beneficial to assign the review team as early as possible in the development process, preferably during the IND submission. For review efficiency and familiarity with the application, the same review team should continuously work on the same application throughout the development to the final review of a NDA/BLA. This provides consistency throughout the entire review process, including pre-submission discussions. If resources prohibit assigning the same review team prior to submission, an information transfer process should be implemented to ensure consistency and acceptance of prior agreements.

9. It is suggested that at a minimum, amendments planned and agreed upon during the pre-NDA/BLA meeting as well as amendments in response to agency information-request letters submitted during the review be included in the first review cycle. In order to minimize impact on agency resources, the IR letter could provide a date by which a response could be included in the review.

10. This guidance only addresses "first-cycle" review of new NDAs or BLAs. There should be some direction and guidance that applies to subsequent cycles. Many of the principles discussed hold throughout additional review cycles. As written, the guidance appears to

suggest that Good Review Management only applies to this first cycle of an original application.

11. Consultants are certainly useful during the review process. The decision-making authority between both internal and external consultants and the review division should be defined up front for the applicant. The consultants should also be included in the pre-submission meetings to assure full agency alignment on submission content. Consultants should be aware of and agree to the review timelines.

12. Good review management principles should include the pre-approval inspection process. Regular communication with the applicant should include the status of inspection requests. This is suggested in the Wrap-Up and Labeling section of the document on Line 1118, but not adequately incorporated into the body of the guidance. Specific comments are included on Line 431.

13. Overall the document tends to suggest different process and language for CBER- versus CDER-regulated products. It would help the applicant to prepare and communicate if the same terminology and process were used. Also, the draft guidance does not encourage consistency across molecules and therapeutic areas.

14. The Common Technical Document (CTD) format should be referenced.

15. The suggested time frames for applicant response may not be sufficient to allow for preparation of a response, e.g., preparation of a response to FDA after a 45-day meeting, but prior to a 60-day decision date. Communicating to the applicant as early as possible would facilitate the review.

16. The success of good review management relies on fully trained staff at FDA, especially the project management skills of the FDA Regulatory Project Managers (RPMs). FDA training is thus critical and should be included in the background discussion and in Section V., Implementation and Evaluation, on Line 1413. It is recognized that reviewer training is an additional activity to GRMPs. It is suggested that training on and adherence to GRMPs should be a component of the performance objectives and evaluation system for review personnel.

17. It is not uncommon for tradename negotiations to delay the launch of potentially life-saving drugs. It is suggested that the tradename assessment process begin at the presubmission meeting and be communicated to the applicant as early as possible but no later than 3 months prior to the first action letter date. This would avoid potential delays in the distribution of the product.

18. Often an applicant references drug master files in an NDA/BLA. During the initial filing period, the applicant should be notified by the Agency if the contents of a master file are known to be deficient. While the information in the master file is confidential and cannot be shared with the applicant, it is not uncommon for an applicant to work with the sponsor of the drug master file to assure that deficiencies are corrected in a timely manner. Thus, if a master file is known to be deficient, this should be communicated to the applicant as soon

as possible, even during a presubmission meeting, so corrective actions can be taken prior to filing.

19. At the end of a review cycle and action letter, it would be very useful for the FDA and the applicant to have a debriefing of the whole application review process and a "Lessons Learned" meeting. The FDA could also issue a "report card" for both the FDA and the sponsor as a mechanism of tracking adherence to GRMPs.

20. Some mention should be made of FDA's ability to post results of reviews (memos, etc.) on the FDA Web sites, and some caution should be given to the reviewers to bear this in mind when writing their review information (with an eye toward the disclosable nature of the information, not to mention pure accuracy of the information).

21. It is acknowledged that some of the proposals may not be consistent with current MAPPs. Ideally, good review practices would be consolidated into one MAPP, and existing MAPPs could be edited to be consistent.

22. The draft guidance includes extensive text on procedure, much of which is available in greater detail in other referenced guidances. This makes it difficult to identify what the agency considers to be GRMPs and what is simply current process. A summary list of the GRMPs would provide useful focus to the document.

23. Where the guidance description includes optional approaches, there should be discussion to guide selection of one option over the other. In other words, the question, "when would it be a GRMP to follow path A instead of path B" should be answered unless all options represent equally good review management principles in all situations. For example, the discussion of use of consultants in the review process gives no guidance to help the reviewer in making a decision to seek a consult, much less when to request an outside consult.

24. Because much of good review management depends on establishing a timeline for the initiation of various activities and their completion, it would be helpful to include in the draft guidance a sample timeline for a typical standard review and a typical priority review which could be used across divisions by RMP, reviewers and all stakeholders, including applicants, for transparency and consistency. We recognize that any example would have to be presented in the context of basic assumptions, and that the timing of certain activities (e.g., issuance of an Information Request or Discipline Review letter) may vary depending on circumstances that are unique to each application. Nevertheless, we believe a model timeline would be a helpful tool for individuals involved in the review planning activity

25. Whether a principle is considered a "good" review management principle (GRMP) depends to a great extent on the objectives or goals that the principle is intended to achieve and what constitutes a measure of success. The draft guidance doesn't clearly define these objectives. Thus, it isn't clear whether the intent of GRMPs is to manage resources efficiently, to promote earliest possible public access to new products by prompt and thorough review and approval, to achieve both, or to achieve some other end. On lines 23-24, the draft guidance states that GRMPs "are intended to promote efficient and consistent *management* of application reviews. If efficient and consistent management of review is

judged only by "actions within goal dates" without regard to increasing the percentage of first action approvals, the public health value of the GRMPs may be small.

The draft guidance makes a point of the prerogative FDA claims *not to review* amendments submitted within the first cycle (even amendments submitted to resolve deficiencies identified early during the filing review - see lines 650-652) but exercising that prerogative guarantees a second cycle review and a corresponding delay in the approval of the product. Likewise, the draft guidance focuses on issuance of action letters on or before the PDUFA goal date. This creates an inevitable need for a second cycle review and, therefore, may not best serve the public health in all cases. On the other hand, good management principles that focus on public health may well stress the importance of the earliest availability of a new therapy and may provide for completion of review in the first cycle even if that means missing the PDUFA goal date while, for example, finalizing labeling negotiations. While the guidance mentions situations in which FDA will postpone review of amendments until a second cycle to take action within the PDUFA goal date, there is no mention of mitigating circumstances under which FDA would choose to miss a goal date to promote earlier access, even though the PDUFA goals have never held FDA to completing 100% of application reviews within the specified time frames.

26. The draft guidance includes "workload priorities" and "workload staffing" among FDA's criteria for deciding whether to extend the clock on an amendment and whether to review an amendment.[1] Under PDUFA, applicants agreed to provide resources to support the review process in exchange for review goals equally applied to all applications. Applicants expect that their applications will be reviewed under the PDUFA on the basis of the merits of the content of their applications and any amendments that are submitted in compliance with regulations and goals. We do not consider it a good review management principle for FDA to discriminate between applications on the basis of workload priorities (suggesting that one applicant's application takes precedence over that of another) or workload staffing (a condition over which the applicant has no control). We recommend that this concept be deleted in finalizing the guidance.

27. Although the document is fairly comprehensive, especially in its reference to other more specific guidances, we see some limitations. For example, the document does not contain information for the role of the FDA Project Manager in the pre-IND phase nor does it provide sufficient guidance on facilitation of communication (other than at the two formal development meetings, i.e. EOP2 and Pre-NDA) in Phase 1-3. PhRMA believes that these phases are equally important in drug development and that communication between FDA and sponsors would benefit by further clarifying the role of the Project Manager and FDA's expectations of Sponsors in these periods. We are also concerned that the practices described seem to make the FDA Project Manager the sole conduit for information exchange. While we believe that this may help to reduce some unnecessary interruptions of an efficient review, we believe that it should still be possible to have direct communication

[1] Lines 155-158 (and other sections identified in "specific comments"): "The FDA may decide to defer review of amendments to a subsequent review cycle for several reasons, including, but not limited to, significant application deficiencies that otherwise preclude approval of the application that are not addressed by the amendment, *competing workload priorities, and limitations in resource availability.*" (Emphasis added)

with other personnel at FDA if mutually desired, and that the Guidelines should address how to facilitate those communications.

PhRMA's specific annotated line by line comments follow in the appendix to this letter. We trust that these comments are useful to the FDA as the Agency moves to a final guidance.

Sincerely,

Allen Goldhammer

APPENDIX - SPECIFIC ANNOTATED COMMENTS

1. Lines 17-21: *"This document is intended to provide guidance to industry and the review staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) on good review management principles (GRMPs) for the conduct of the first-cycle review of a new drug application (NDA), a biologics license application (BLA), or an efficacy supplement under the Prescription Drug User Fee Act of 1992 (PDUFA)."*

   Recommendation: PhRMA suggests adding the following sentence: *"Similar principles laid out in the guidance document should also apply to subsequent cycle reviews."* This addition would encourage the applicant and the agency to continue the collaborative approach to review applications and ensure minimal change in review team constitution and continuity. Although this is alluded to in "Cycles of review" (Line 1384), it needs emphasis, especially with regard to continuity.

2. Lines 21-22: *"The GRMPs in this guidance are based on the collective experience of CDER and CBER...."*

   Recommendation: An appendix with illustrative examples of GRMP best practices both within the agency and between the agency and industry would be useful and would allow some consistency.

3. Lines 47-49: *"This guidance is expected to lead to greater consistency and efficiency of the review process within individual review divisions, across review divisions, and between CDER and CBER."*

   Recommendation: PhRMA suggests revising the text to read as follows: *"This guidance is expected to lead to greater consistency and efficiency within and across review divisions, and to enhance the transparency of the review process between the review team and the applicant."* With a better understanding of the review process and schedule, the applicant can better partner with the review team to meet the PDUFA goals.

4. Lines 62-63: *"...the FDA is dependent on the availability of adequate resources..."*

   Recommendation: PhRMA suggests changing the text to read: *"...adequate resources are required..."* The guidance should put forth an expectation that the agency will ensure adequate resourcing, especially since they will receive more lead time from the applicants as encouraged in the guidance. Such encouragement will allow PDUFA timelines to be met and ensure GRMPs.

5. Lines 74-79: *"Additional Agency documents are available and should be consulted to supplement the information in this guidance, including staff instruction documents (i.e., CDER's Manual of Policies and Procedures (MAPP), and CBER's Manual of Standard Operating Procedures and Policies (SOPP)) and guidances for industry and review staff."*

   Recommendation: Reference should be made to Appendix B.

6. Lines 93-95: *"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 attempt to resolve readily correctable deficiencies in the application."*

   Recommendation: This sentence discusses only the issue of time. The primary focus of GRMPs is to lead to greater efficiency of the review process, as noted in Lines 47-49. PhRMA suggests adding the concept of improved efficiency in this sentence, both within the agency as well as in interactions between agency and applicant.

   In addition, use of terms such as "readily correctable deficiencies" (Line 95) and "significant deficiencies" (Line 103) are open to interpretation. Inclusion of definitions can help differentiate the two situations.

7. Lines 105-106: *"...provides the applicant with timely notification of such deficiencies. Often, timely notification of correctable deficiencies allows the applicant..."*

   Recommendation: FDA should be encouraged to issue the action/correspondence as soon as possible after completion of the review. In many instances the review may be completed prior to the Action Due date. Waiting until the actual Action Due date to issue a CR letter may not necessarily be "timely."

8. Lines 113-116: *"The GRMPs emphasize the importance of (1) a strong interdependence among the primary FDA review team, (2) frequent interactions between the primary review team and supervisory reviewers, and (3) the critical role of effective project management in the successful completion of the first-cycle review."*

   Recommendation: A fourth aspect to a successful review is the development and communication to the applicant of key milestones in the review timeline. If the applicant understands the agency's key milestones of the review timeline, the applicant can partner with the review team to meet the PDUFA goals. The interactions between the primary and supervisory reviewers should be ongoing to allow sufficient time to identify and investigate potential issues with the application and come to consensus on resolution.

   PhRMA suggests revising the text to read as follows: *"The GRMPs emphasize the importance of (1) a strong interdependence among the primary FDA review team, (2) development and communication of key milestones of the review timeline to the applicant, (3) continuous interactions between the primary review team and supervisory reviewers, and (4) the critical role of effective project management in the successful completion of the first-cycle review."*

9. Lines 134-135: *"A complete application should contain all required and expected information to support approval of the requested claims, labeling, and dosage forms."*

   Recommendation: PhRMA suggests adding this sentence to the end of Line 135: "*This would include information agreed upon in prior communications with the agency as well as information contained in FDA guidances."*

10. Lines 145-147: *"The applicant is strongly encouraged to manage the drug development timeline in a manner that leads to submission of a complete application, with the exception of safety updates, for FDA review."*

    Recommendation: PhRMA suggests revising the text to read as follows: *"...with the exception of safety and stability updates, for FDA review."* Additional stability data should be provided during the review process to allow an adequate assessment of product integrity.

11. Lines 149-151: *"Such requests and agreements should generally be limited to situations when the FDA agrees that there is a valid public health urgency to expedite the availability of an important new product."*

    Recommendation: PhRMA suggests revising the text to read as follows: "...*to expedite the availability of an important new product or claim (sNDA)."*

12. Lines 153-154: *"The FDA retains the authority to decide whether to review application amendments, solicited or unsolicited, submitted during the first review cycle."*

    Recommendation: FDA should honor any agreements made in presubmission discussions regarding the submission of additional data/information during the review, and commit to a first-cycle review of any planned amendments agreed to in presubmission discussions. Such agreements should not be subject to change (e.g., resulting from changing priorities or workloads of the review division or a change in primary reviewers or management). If solicited or unsolicited amendments will not be included in the first review cycle, the applicant should clearly understand this prior to submitting the amendment. Any changes could have a major effect on timelines and a significant impact on the sponsor's development plans. This information will assist the applicant in prioritizing the response to facilitate the overall submission review and approval.

    PhRMA suggests revising the text to read as follows: *"The FDA retains the authority to decide whether to review application amendments, solicited or unsolicited, submitted during the first review cycle, with the exception of those planned and agreed to in previous discussions with the applicant. In information request letters, FDA will notify the applicant under what circumstances, for example response timing, the amendment will not be reviewed during the first review cycle."*

13. Lines 154-158: *"The FDA may decide to defer review of amendments to a subsequent review cycle for several reasons, including but not limited to... competing workload priorities, and limitations in resource availability."*

    Recommendation: Review deferral due to significant deficiencies is understandable. However, with regard to the challenges of balancing workload and resources, the latitude that FDA is allowing itself seems unfair *for planned amendments*. If a firm submits a planned amendment on time and within scope, every effort should be made to review that amendment during the first review cycle.

    It is the expectation of the applicant that the agency provide adequate resourcing. Such caveats may allow the agency to not meet PDUFA timelines. The PDUFA fee system is

intended to alleviate resource constraints and support application review. It is not clear how FDA will define "competing workload priorities and limitations in resource availability."

14. Lines 158-159: *"It has been FDA's experience that submission of a complete application leads to the most efficient review process and shortest approval time."*

    Recommendation: PhRMA suggests revising the text to read as follows: *"This does not imply that use of a rolling submission for 'Fast Track' designated products may be less efficient."*

15. Lines 159-161: *"In some cases, submitting a complete application may require a decision by the applicant to delay initial submission beyond a corporate target date."*

    Recommendation: The reference to corporate target dates appears to represent a supposition by FDA that corporate directives determine the date for filing an application, regardless of factors that may affect progress of the development program. This is unfounded and, therefore, it is inappropriate to include this language in regulatory guidance. The comment should be deleted in preparing the final guidance.

16. Lines 165-177: *OVERALL PRINCIPLES – Communication between FDA and Applicant*

    Recommendation: The draft guidance is missing some time points of communication between FDA and the applicant. PhRMA suggests adding the 45-day presentation, 74-day communication, and face-to-face 90-day meeting, as well as EOPI meetings. EOPI meetings, although not mentioned in the PDUFA meeting guidance, are now being granted by FDA. The draft guidance could also encourage both written and verbal responses to pre-submission meeting discussion topics. For some issues, written responses by FDA will suffice, while others require discussion between the applicant and FDA. This practice, which promotes more efficient sharing of information and is sometimes used by FDA, should be encouraged in the current guidance.

17. Lines 168 – 171: *"Such communications allow the FDA to provide valuable guidance and advice regarding the applicant's drug development program and, during the review of a marketing application, to identify deficiencies that may require the applicant to submit additional analyses or data."*

    Recommendation: PhRMA suggests changing the text to: *"Such communications allow the FDA the opportunity to provide valuable guidance…"*

18. Line 187: *"A. Presubmission"*

    Recommendation: "Presubmission" is a confusing term, as it can be interpreted as the review process when information is presubmitted as defined in 21 CFR 314.50 (d)(1)(iv). In other guidance documents, this period is normally referred to as "Development." PhRMA suggests revising the title to: *"A. Development Activities."*

19. Lines 193-202: *"The FDA review staff should understand the critical importance of effective and timely communication between the review division and the applicant throughout the IND*

process. The FDA review staff are uniquely qualified to provide valuable scientific and regulatory advice to the applicant during the drug development phase. This advice can result in more efficient and robust drug development programs, furthering FDA's public health mission to make safe and effective drugs and biologics available to the American public in a timely manner. Effective communication between the FDA and the applicant during the IND phase can also lead to identification of potential filing and review issues that can then be addressed by the applicant before the application is submitted for review."

Lines 204-207: "To provide the foundation for productive interactions with the applicant, FDA review staff should monitor closely each assigned IND to maintain a good working knowledge of the product characteristics, the proposed development strategy, and the applicant's proposed indication(s) for approval."

Recommendation:
(1) PhRMA suggests adding text to instruct FDA reviewers that all attempts should be made to provide sponsors with "timely feedback" to create "effective communication." A statement should also be added regarding the quality of IND amendments – the better the quality/ clarity, the faster the feedback. Also, at which point in time will a sponsor be notified if their study is to be placed on hold since there is no established timeframe for commenting on IND submissions apart from the established 30 day initial safety review for an IND. A target review time; e.g., 6-8 weeks, for non-hold comments, or for comments on subsequent protocol amendments or new protocol submissions, would facilitate the sponsor's decision to proceed at risk with no Agency input or to halt development pending input.

(2) With respect to proposed indications mentioned in Lines 204-207, other elements beyond the proposed indication that would foster more productive interactions during the development phase should be considered (e.g., the role of the developing label as the driver could be discussed in this part of the document).

20. Lines 209-221: Milestone Meetings

Recommendation: The document would benefit from a discussion on the communications process for Subpart H drugs (or at least refer to a separate guidance as appropriate).

21. Lines 211-212: *"Review divisions should also explicitly encourage the applicant to take advantage of end-of-phase 2 (EOP2) and pre-NDA/BLA meetings…."*

Recommendation: Missing from the draft guidance is an emphasis on meetings prior to EOP2. There should be comprehensive discussion of possible times of communication between FDA and the applicant. PhRMA suggests adding discussion on pre-IND, IND, and EOP1 meetings, as well as more formal discussions (meetings) regarding other critical development issues that involve CMC or facility issues (perhaps referring to Type A and Type C meetings, to tie into the guidance on meetings).

22. Lines 217-218: *"Meetings during the IND phase and SPA submissions are invaluable opportunities for the review division and the applicant to review…."*

Recommendation:

(1) PhRMA suggests revising the text to read as follows: *"Meetings during the IND phase and SPA submissions are invaluable opportunities for the review division, consultants (as appropriate), and the applicant to review...."* For general agreement and consistency, it is beneficial to include consultants in meetings, especially in the presubmission meetings.
(2) The SPA guidance does not guarantee a meeting with FDA. Will FDA also update the SPA guidance to ensure a meeting if needed? It is suggested that provision should also be made for *ad hoc* developmental meetings.
(3) Reference to FDA's guideline entitled, *Formal Meetings with Sponsors and Applicants for PDUFA Products,* is also suggested.

23. Lines 227-228: *"The pre-NDA/BLA meeting generally should be scheduled 6 to 12 months prior to the anticipated date for application submission."*

Recommendation: PhRMA suggests adding the following text: *"Use of FDA consultants should be identified and included in the pre-NDA/BLA meeting preparation,"* so that consultants can be included in the presubmission meetings.

24. Lines 232-235: "In preparing for the pre-NDA/BLA meeting, the review division should attempt to address any specific questions raised by the applicant in the meeting background package."

Recommendation: The review division should be able to address specific questions for the pre-NDA/ BLA meeting. PhRMA suggests changing the text to read: "In preparing for the pre-NDA/BLA meeting, the review division should address any specific questions raised by the applicant in the meeting background package and provide written responses or verbal feedback to the sponsor's questions before the meeting actually takes place." This can lead to a more focused meeting, or even cancellation of the meeting if the answers are clear and obviate the need for a meeting. The Oncology Division does this routinely.

25. Lines 237-238: *"...summary information provided by the applicant in the meeting background package."*

Recommendation: PhRMA suggests revising the text to read as follows: *"...summary information provided by the applicant in the meeting background package and EOP2/SPA agreements."*

26. Lines 242-245: *"New initiatives under the PDUFA goals, including enhanced preapproval attention to risk management by the FDA and the applicant, and two pilot programs to explore the continuous marketing application (CMA) concept, are underway and are the subject of separate guidances."*

Recommendation: References to the separate guidances should be specific and listed in Appendix B.

27. Lines 252-253: *"The Agency emphasizes that the quality and completeness of NDAs, BLAs, and efficacy supplements at the time of submission is critical...."*

Recommendation: PhRMA requests clarification on the following: Does FDA expect that all studies be complete at the time of pre-NDA/BLA? Will FDA be amenable to presentation of new data/information at the meetings?

28. Line 261: *Milestone Meetings*

Recommendation:
(1) PhRMA recommends adding the following sections: (a) "Other Key Interactions during Development" since these types of interactions are also important during the review process. (b) A section that includes FDA recommendations on how to more formally resolve discrepancies between the agency's meeting minutes and the sponsor's, following a milestone meeting.

(2) Lines 261-292 vs. Lines 211-238*: 2. Applicant Focus a. Milestone meetings versus 1. FDA focus a. Milestone meetings*

While the FDA addresses the level of preparedness required of a sponsor for milestone meetings (Applicant focus), there is nothing in the *FDA focus* that addresses the level of preparedness for FDA staff to provide helpful feedback to a sponsor. The level of preparedness for meetings varies greatly between teams and among members of teams. The guidance should outline some minimum expectations for FDA staff.

29. Lines 275-276: *"... it is recommended that the applicant present a clear, concise background package...."*

Recommendation: PhRMA suggests replacing *"background package"* with *"briefing document,"* so as to use standard terminology.

30. Lines 278-282: *"The pre-NDA/BLA meeting package should contain a comprehensive summary of all relevant data generated during the development program, identify pivotal trials and primary endpoints, and discuss all critical and potentially critical issues (i.e., any issues that may affect FDA's ability to review the application and/or approve the product)."*

Discussion:
21 CFR 314.47(b)(2) - *"'Pre-NDA' and 'pre-BLA' meetings* states in part, *"The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application.... ...(T)he sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information: (i) A brief summary of the clinical studies to be submitted in the application; (ii) a proposed format for organizing the submission, including methods for presenting the data; (iii) information on the status of needed or ongoing pediatric studies; (iv) any other information for discussion at the meeting."*

As stated on lines 224-227 of the draft guidance,[2] and underscored in the language of the regulation, the focus of a pre-NDA/BLA meeting is on the format and presentation of the data in the marketing application. The pre-NDA/BLA meeting is not intended to be a detailed discussion of study results. The expectation of a comprehensive summary of "all relevant data generated during the development program" in the background package for a pre-NDA/BLA meeting is at odds with the primary purpose of the meeting. Indeed, a comprehensive summary may not be available at the time of preparation of the pre-NDA/BLA meeting background document since the data analysis may not be completed in the timeframe which would allow for the pre-NDA/BLA meeting to take place.

Recommendation: Sponsors generally develop and submit mock data tables in background documents for pre-NDA/BLA meetings in lieu of tables displaying the actual data in order to show their proposed data layout in the absence of the actual data generated by the program. This has proven to be an effective strategy. PhRMA recommends inclusion of such a strategy in the final guidance document. Additionally, it is suggested that the term *"comprehensive"* be replaced with *"focused."* It may not be possible to be both concise (Line 276) and comprehensive (Line 279), but it is possible to be concise and focused.

31. Lines 284-285: *"The applicant is strongly encouraged to describe both the strengths and the weaknesses of a proposed application."*

Recommendation:
(1) To ensure that more relevant information is provided by the applicant, PhRMA suggests revising the text to read as follows: *"The applicant is strongly encouraged to describe both the strengths of the proposed application and the difficulties encountered in development. Sponsors should point out issues they faced in addressing the regulations and guidelines for approval, and how these difficulties were addressed. Unexplained results or findings, based upon primary or secondary endpoints, safety assessment, or subset analyses should be identified with a provision of the sponsor's assessment of their relevance."* In addition, a post-NDA submission meeting should be considered, as has been utilized by the Oncology Division.

(2) This section implies a scientific discussion of data results. As noted above, the draft guidance and current regulations describe the pre-NDA/BLA meeting as being one which deals with the process and the formatting of the application. This paragraph seems to be inconsistent with the earlier statement of goals for the meeting. Additionally, it would seem inappropriate to expect reviewers to engage in a detailed discussion about the scientific issues and data at this time point, although the issues could be identified in the context of data presentation.

The draft guidance appears to confuse the purpose of a pre-marketing application meeting by recommending the inclusion of a comprehensive summary of data in the background package and implying that the meeting should include discussion of the merits of the application which, presumably, would be data driven. Where unexpected outcomes occur

---

[2] "The meeting should focus on the format of a proposed application and creating a shared understanding between the FDA and the applicant of an acceptable content to support initial planning for efficient review management."

during the development of a product, it would seem to be a good review management principle to encourage sponsor-FDA interaction to address their implications rather than wait until the pre-NDA/BLA meeting to do so. Further, given the time available for the pre-NDA/BLA meeting (1.5- 2 hours), engaging in any scientific discussion may take a significant amount of time thereby pre-empting achievement of the primary goal of the meeting.

32. Lines 284 - 292

Recommendation: The Agency recommendation is that sponsors plan for pre-NDA meetings 6-12 months prior to a submission. However, on page 7 the guidance suggests that the applicant should "describe both the strengths and weaknesses of a proposed application." Practically speaking, the operational details of data presentation can (and probably should) be worked out with the Agency 6-12 months prior to a submission. But it is often the case that the pivotal trial data will not be available for a thorough discussion of the "strengths and weaknesses" in this timeframe. PhRMA suggests that the guidance acknowledge this and detail options available to the sponsor for another meeting to discuss "strengths and weaknesses" prior to a sponsor decision to submit.

33. Line 294: *Risk Management Plan*

Recommendation:
(1) PhRMA suggests adding reference to the specified guidance in a footer.
(2) It appears from this draft guidance that FDA is expecting detailed discussion of the risk management plan as part of the pre-NDA/BLA milestone process. This is contrary to FDA's Talk Papers, in which they suggest discussion of this sort at the EOP2 meeting (which has been the standard practice to date). PhRMA requests clarification.
(3) PhRMA requests that the FDA clarify whether the risk management plan referred to in this section is an agency expectation. Will the format of such a plan be described in the forthcoming guidance document?

34. Lines 306-311: *"Between the pre-NDA/BLA meeting and the time of submission, the applicant is encouraged to inform the review division if plans for the content or format of the application change significantly. In addition, the applicant should provide the review division with updates regarding the timing of the planned submission. Such information is useful to the review division in assigning projects and effectively managing limited resources."*

Recommendation:
(1) PhRMA suggests revising Lines 307-308 to read as follows: *"...to inform the review division if plans for the content or format of the application change significantly, and the reasons for the change."*
(2) It would be useful to FDA staff and to applicants if the guidance expanded this discussion to include a description of mechanisms that are in place to utilize the information described in lines 306-311 in assigning projects and managing resources.

Lines 308-309: *"In addition, the applicant should provide the review division with updates regarding the timing of the planned submission."*

Recommendation: For rolling submissions, the guidance should detail the information the sponsor should provide to FDA regarding submission strategy (e.g., which parts of the application will be submitted, in what sequence, and when), how they will be processed within FDA, how a "complete application" will be assessed, and how this process may differ from that for assessing a non-'Fast-Track' submission. Cross-references to other relevant guidances would also be helpful. Similarly, with the current trend towards the submission of electronic applications, it is suggested that there be some mention of the particular contingencies and differences from paper applications in the submission acceptance and review processes, with cross-referencing to specific guidances.

35. Lines 317-318: *"...the division should inform the applicant of the deficiencies in a clear and timely manner."*

Recommendation: In the spirit of the GRMP guidance put forth in the background section, PhRMA suggests that a more specific definition of "a timely manner," be provided and/or engage in continuous dialogue with the applicant.

36. Line 318: *"The applicant should be advised that, if uncorrected,..."*

Recommendation: PhRMA suggests revising the text to read as follows: *"The applicant should be advised in writing that, if uncorrected,...."*

37. Lines 329-331: "The FDA's recommendations are best followed in their entirety; partial adherence to FDA's recommendations may significantly undermine the potential benefit of presubmission communications."

Recommendation: This language should be modified, as it implies there is only one way to prepare the application - the way that FDA has told the applicant to do it. The sentiment should be that there should be a full understanding of FDA's issues or concerns and there should be an agreement in terms of how to resolve them, rather than an expectation that an applicant should blindly follow the FDA's recommendations, particularly if the applicant believes that there are mitigating factors that would support an alternative approach. PhRMA suggests rephrasing Lines 329 – 331 to bring forth a spirit of mutual learning.

38. Lines 339 – 341: *"During the application receipt process, the application content is assessed, and the application is assigned to the appropriate review team members."*

Recommendation: PhRMA recommends that members of the review team be included in the filing letter.

39. Line 341: *"Review team roles and responsibilities are clarified during this process."*

Recommendation: It is industry experience that in addition to the review team roles, the roles of the supervisory team, consultants, and signatories need clarification. PhRMA suggests revising the text to read as follows: *"Review team, supervisory team, consultant and signatory roles are clarified during this process."*

Lines 343-345: "*Upon receipt in the Central Document Room in CDER or the application review division in CBER, an NDA or BLA is assigned an application number. In some cases, a number can be assigned prior to submission if requested by the applicant.*"

Recommendation: It is recommended that "in some cases" be defined. Clearly, two different mechanisms are described: pre-assigned numbers and numbers assigned upon receipt. The guidance should indicate whether these mechanisms are equally "good" review management principles or describe circumstances when one method is preferred over the other. Pre-assignment of application numbers appears to have several advantages by allowing the sponsor to incorporate this important identifier into various reports and application documents.

PhRMA also suggests that the guidance define "*receipt in the Central Document Room*" as the same calendar day the application physically is delivered to the CDER DCR or the CBER DCC, e.g. applications delivered within business hours must be logged in on the same day.

40. Lines 345-349: *"The submission is date-stamped on the day of receipt, and payment of any applicable user fee is due on that day. The application is then transferred to the review division document room (DDR) in CDER. Agency manuals delineate for FDA review staff the current policy and procedures for application processing."*

Recommendation: This draft guidance only addresses the CDER CDR, not the CBER Document Control Center. This is not always true with regard to the CBER DCC - as can be shown from discrepancies in signed AirBill receipts and date of submission issued by FDA. Sponsors currently experience significant difficulties in dealing with the CBER DCC. There appears to be a significant issue with a delay in the log-in of submissions (such that date of receipt and start of time clock are not what the sponsor expects), and an even more significant delay (sometimes up to 2 weeks) in the routing of submission for review to the review divisions. Such delays can adversely affect the review process for both the reviewers and the sponsors.

41. Lines 351-352: *"Once received in the review division, an application should be assigned to a regulatory project manager (RPM) as soon as possible."*

Recommendation: While it may be a good review management principle to complete certain actions "as soon as possible," the phrase is too vague to be of use in truly defining a timeframe beyond which the principle is violated. The guidance should be screened for this phrase and wherever it appears, consideration should be given to including a recommended range of time that Center management considers in keeping with good review management. In addition, it may be useful to include a discussion of the guidance of how such assignment might be made if the RPM assigned to the IND is on extended absence when the application comes in (e.g., sick leave, jury duty, vacation). Clearly, "assignment" to the RPM could be made "as soon as possible" but effective processing of the application would not commence until his or her return.

42. Lines 352-354: *"The RPM should determine whether the applicant has complied with all required user fee payments and, if so, the review clock starts the day of application receipt."*

Recommendation: PhRMA requests clarification on the following: If the clock starts on the day of receipt, should it be assumed that the check for user fees is conducted at the same time? How can the final determination of the applicant user fee status be made and time clock started on the date of receipt?

43. Lines 360-361: *"With the commencement of the review clock, multiple, simultaneous activities should begin promptly to maximize the time allotted for each activity."*

Recommendation: PhRMA suggests that the guidance reflect that the Regulatory Project Manager (RPM) prepare an acknowledgment letter communicating to the sponsor: the assigned NDA number, the official date of receipt, the anticipated filing date, the preliminary therapeutic classification (subject to final determination and confirmation by the filing date), and the RPM contact information. We believe that an appropriate target for completing the acknowledgement letter is 14 calendar days following receipt of the application.

44. Lines 365-373: *"To ascertain the completeness of the application on its face, the RPM should conduct an administrative review; including ensuring that financial disclosure information has been provided by the applicant. Deficiencies identified during this review should be communicated to the applicant promptly to enable immediate correction if possible. Administrative issues can be sufficiently substantive to warrant a refuse-to-file action (e.g., when a significant section of the application is missing). This review is the NDA Regulatory Review in CDER and is finalized after the filing meeting with the attachment of filing meeting minutes."*

Recommendation: It is not clear why financial disclosure information is singled out (Line 366) as an item of concern. PhRMA suggests deleting the last part of the sentence, such that the text simply reads: *"...conduct an administrative review."* Alternatively, the guidance should provide a complete listing. To be useful for sponsors in improving submissions as well as to RPMs expected to conduct the administrative review, and to establish consistency across divisions, the components of administrative review under GRMPs should be outlined. It may also be helpful to clarify that other review team members will participate in the review.

In addition, the draft guidance states that deficiencies identified in the administrative review should be communicated to the applicant promptly. It then notes that the review is finalized *after* the filing meeting. It is not clear whether communication of deficiencies to the applicant is expected to take place before or after the review is finalized[3]. If the deficiencies are communicated to the applicant before the review is finalized, is concurrence by the Chief of the Project Management Staff or other division official required prior to communication with the applicant? These details should be incorporated into the final guidance.

---

[3] The following statement from lines 533-535 suggests that the deficiencies are conveyed before finalization of the review: "During the application receipt process, the FDA will routinely convey readily correctable issues to the applicant in a timely manner as they are identified with the expectation that they should be addressed quickly."

45. Lines 379-380: *"The primary review team should be assigned as soon as possible after receipt of a new application."*

    Recommendation: The guidance should specify a time frame (range) for the assignment of the review team, which meets GRMPs. PhRMA suggests revising the text to read as follows: *"The primary review team should be assigned prior to the presubmission meeting. If new team members are assigned, previous commitments should be honored as part of a formal information transfer process."* This revision should be moved to the presubmission discussions in the paragraph starting on Line 223.

    It would also be useful information to state in the guidance who makes the assignment decision. For example, does each discipline team leader or supervisor make the assignment or is this the responsibility of the Division Director? Are any primary team members "automatically assigned" based on either their involvement in the IND or their assignment to handle a specific class of products within a division? How (and when) is the sponsor notified of the identity and contact information of the RPM? It would also be helpful to sponsors to receive a list of the names, titles, disciplines/roles of the review committee upon assignment (in addition to the primary CSO contact).

46. Lines 381-383: *"However, in certain cases new or additional reviewers may be assigned as dictated by workload, competing priorities, application complexity, or review discipline staffing."*

    Recommendation: The focus of this guidance should be on *good principles* for managing the review process, not expedients made necessary by unanticipated events. It is not clear how the above cited statement reflects GRMPs. When workload, competing priorities or staffing issues dictate the assignment of new reviewers, it seems more likely that crisis management has taken the place of GRMPs. The assignment of additional reviewers in the case of application complexity, on the other hand, may be a good principle but the guidance would be improved by providing examples of the kinds of complexity that should lead Division management to consider this option.

47. Lines 386-387: *"Membership of the core team is dictated by the specific content of each application."*

    Recommendation: The review of a section of the application should be limited to review by the Center/Division with the review authority. Having multiple reviewers of the same data set is not an efficient review process. PhRMA suggests adding the following text: *"If multiple FDA review Divisions and /or Centers are included in the review of an application (i.e. combination products), FDA should determine which center or division will have ultimate review authority for each portion of the submission and thus be assigned responsibility to review and summarize deficiencies into DR letters."*

48. Lines 398-409: *Consultants*

    Recommendation:
    (1) The bulleted list should be complete and represent all parties that may be involved as consultants. It would be beneficial to include the consultants in the presubmission meetings

and the pre-filing assessments discussed on Line 217. PhRMA suggests adding to the list the following: Environmental Assessment, Microbiology, Virology, Office of Compliance, Office of Drug Safety (ODS), Division of Medication Errors and Technical Support (DMETS), and Additional Centers.
(2) Without further detail or, perhaps, inclusion of some hypothetical examples, when it would be a good review management approach to seek consultation on the standard application technical section reviews cannot be determined from this statement. While one might surmise when a clinical consult to another division may be useful (for example, to the Cardio-Renal Division for a product that has some effect on QTc interval), it is less easy to speculate about the necessity for consults involving the other review disciplines. In addition, the timing of a decision to request a consult on an issue, as well as whether the primary and consult reviews are conducted concurrently or consecutively, are review management issues that are not addressed in this section [Lines 423-424 state only that "Reviewers should identify the need for consultant input as early as possible in the review process..."]. Further, the guidance only indirectly addresses whether "consultants" includes the option to use outside consultants (see Lines 425 - 426) as well as internal consultants. Discussion to guide reviewers on when good review management calls for consideration of the use of an outside consultant would be helpful.

49. Lines 413-417: *"Postmarketing drug safety staff from CDER...and CBER...are expected to work in collaboration with the review division staff in reviewing RMPs* [Risk Management Plans] *and providing expert advice to applicants and the review divisions."*

Recommendation: This language suggests that Postmarketing Drug Safety staff are available to provide advice on Risk Management Plans directly to applicants as well as to review divisions. It is recommended that all advice on RMPs flow through the review division to assure that agreements are understood by all parties.

50. Lines 421 – 426: *"The consult process may also involve seeking expertise from other review divisions, FDA centers, and in some cases, outside experts (e.g., special government employees from the professional community). Reviewers should identify the need for consultant input as early as possible in the review process so the appropriate consultants can be identified promptly and, if necessary, screened for any potential conflicts of interest."*

Recommendation: PhRMA suggests discussing consultations within the agency such as OPSS, and with other divisions - such as DCRDP for QT issues. This allows for a comprehensive discussion on how to manage consultations within the agency. It is also suggested that applicants be allowed to recommend possible external consultants to the agency at the pre-NDA meeting. Consultants who may be familiar with the data will increase the efficiency of the review process. In addition, a similar statement was recommended to be included in Section IV.A. (Presubmission – Line 187) regarding combination products. There is no suggestion as to specific placement.

51. Line 428: iii. Requests for Inspection

Recommendation: This section should clarify that additional requests to the sponsor will come from DSI. PhRMA also suggests adding the following text to the end of the

paragraph: *"The RPM should track the status of inspections and communicate with the applicant regarding the decision to inspect and the timing."* Since the status or completion of an inspection can impact the review cycle, the review team should communicate clearly and effectively with those parties involved in inspections.

Additionally, with the consolidation of several CBER divisions into CDER, will the two Centers continue to have separate procedures for inspections?

52. Lines 430 – 431: *"Requests for inspections of manufacturing facilities and research sites should be made early in the review cycle and, optimally, prior to the filing date."*

Recommendation: *PhRMA suggests revising the text to read:* "Requests for inspections of manufacturing facilities and research sites should be made at the filing date."

53. Lines 442 - 443: *"A decision regarding the review priority (i.e., priority or standard) for NDAs, BLAs, and efficacy supplements should be made as soon as possible following receipt of the application."*

Recommendation: PhRMA suggests changing *"as soon as possible"* to *"immediately after FDA's 45-day meeting or earlier (e.g. pre-NDA meeting)."*

54. Line 449 - 453: "*The decision should be based on the merits of the product and the application data and should not be contingent on internal FDA considerations such as competing workload or currently available resources in the review division or on whether the subject product was designated fast track during the development phase."*

Recommendation: PhRMA suggests that this section clarify the link (or lack thereof) of "fast track" designation and "priority review."

55. Lines 454-455*: "Agency manuals delineate for FDA review staff the current policy and procedures for assigning review priority."*

Recommendation: PhRMA strongly suggests creating uniformity between the Centers and recommends the use of CDER's definition. In reviewing the criteria for priority review, the Centers differ on what is considered to merit a priority review.

CDER's definition: "The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation."

56. Lines 457 - 461: "*In some instances, a preliminary designation of review priority may be made prior to submission. However, an official decision about review priority can be made only after the application is received for review. In some cases, a presubmission*

assessment of application review priority may be changed once the application is actually submitted for review."

Recommendation: From this discussion, it is unclear whether it is considered to be a good review management principle for applicants to request (and the agency to make) preliminary designation of review priority. The admonition with respect to the preliminary nature of such a designation and the possibility for it to be changed suggests little benefit to either the applicant or the agency from preliminary designation. Guidance on GRMPs should distinguish between review practices that are possible but not necessarily "good" in the sense that they should be encouraged because of their beneficial effect on the review process. Practices that reflect good principles should be the focus of the guidance. Practices that are merely possible but are not encouraged are, perhaps, best not discussed lest their appearance in the guidance suggests that they are recommended.

The Guidance should provide additional information on the circumstances under which the Review Division may make a preliminary designation. The process for conveying the designation to the sponsor should be discussed. Must the sponsor specifically request the preliminary designation? If so, at what time point should the sponsor request it?

57. Lines 464-466: *"Once the decision is made to assign a priority review, that designation should not be changed during the first review cycle, regardless of findings during the review."*

Recommendation: PhRMA suggests revising the text to read as follows: *"Once the decision is made to assign a priority review, that designation cannot change."* Clarification is needed on the designation of a priority review during the review cycle. The decision of a priority review only impacts the initial review clock. Review times for subsequent amendments are the same regardless of review status.

58. Lines 477 - 478: *"A decision regarding the signatory authority for an application should be made as soon as possible following receipt of the applications."*

Recommendation: The final guidance should include a recommended time frame to give meaning to the phrase "as soon as possible." It would also be helpful to include a statement on who is responsible for making this decision and whether a specific decision is made for every application or whether it is assumed to follow the general agency policy that is summarized in this section. In addition, we believe the guidance should stipulate that the RPM should notify the applicant when a decision to raise an application to a higher level signatory authority is made.

59. Lines 498-600: Substantive deficiencies in applications

Recommendation: PhRMA suggests adding an appendix with the most common deficiencies that CDER and CBER have noted in their past reviews. This allows for better understanding of the possible flaws, and applicants can then avoid these flaws in their applications, resulting in greater efficiency.

60. Lines 502 - 504: *"The filing meeting for a standard application should be scheduled in time to finalize and communicate the filing decision by the 60-day filing date, often placing the filing meeting approximately 45 days after receipt of the application."*

    Recommendation: By implication, specifying that this timing applies to "standard" applications suggests that a different time frame may apply to "priority" applications. The guidance should describe GRMPs for filing meetings on priority applications as well.

61. Lines 504-507: The document states that during filing review, if the Agency "identifies serious deficiencies that may warrant a refuse-to-file action, the applicant should be informed of these deficiencies in a timely manner, generally no later than day 45 of the filing review." (Lines 667-669) However, the document also states that filing meetings occur "approximately 45 days after receipt of the application. This timing should allow the applicant sufficient time to resolve readily correctable filing issues...that might warrant a refuse-to-file decision." (Lines 504-507)

    Recommendation: The first passage implies that the applicant will be informed of potential refuse-to-file deficiencies by day 45, which seems reasonable. However, the second passage implies that filing meetings, which occur around day 45, may apparently generate additional refuse-to-file deficiencies. This allows very little time for a firm to respond before the 60 day filing date. This apparent inconsistency in the document should be addressed. It is suggested that nearly all refuse-to-file deficiencies be identified and communicated to the applicant within the first 45 days, and that the filing meeting should rarely uncover deficiencies significant enough to warrant a refuse-to-file action.

62. Lines 512 - 515: *"To help ensure that the application receipt process proceeds smoothly, the applicant should prepare and submit an application in accordance with presubmission recommendations from the FDA, providing a complete application as previously discussed."*

    Recommendation: In view of the emphasized importance of presubmission meetings between the applicant and the agency to discuss and agree on elements of content and format of an application, PhRMA recommends revising the text to read as follows: *"To help ensure that the application receipt process proceeds smoothly, the applicant should prepare and submit an application in accordance with presubmission agreements between the FDA and the applicant, providing an organized and properly indexed application as previously discussed. This may include agreed upon rolling submission."*

63. Line 519: *"Throughout the application receipt process and continuing throughout the entire review..."*

    Recommendation: PhRMA suggests adding the following text prior to Line 519: *"Prior to the filing of the application, near day 45, the FDA and the applicant should schedule the NDA/ BLA Presentation meeting. During this meeting, the applicant presents a summary of the application to the FDA review team and responds to their specific questions. This open dialogue promotes a clear understanding of the key findings and content of the application and may identify and/or resolve possible deficiencies."*

64. Lines 517-531: e.3. Communication between FDA and Applicant

Recommendation: It is agreed that communication and inquiries regarding application status should be directed to the RPM. It is also agreed that the use of secure e-mail with copies sent to the RPM and the relevant reviewers is very effective. However we suggest that primary reviewers be allowed to contact the applicant directly with brief requests and questions, without incurring the delay of going through the RPM to set up and participate in a teleconference. PhRMA therefore suggest adding the following text to the end of the sentence: "*On the occasion that the reviewer contacts the applicant directly to inquire about a specific question, the applicant can respond directly to the specific issue only. It is the responsibility of the reviewer to inform the RPM of the interaction.*" Likewise, if the sponsor has a need for timely clarification on an FDA request or wishes to provide a brief answer to a quick question, we believe the sponsor should be allowed to contact the reviewer directly if the reviewer has indicated the interaction would be acceptable to him or her. This process has worked extremely well with CBER interactions in the past.

65. Line 533: *"During the application receipt process, the FDA will routinely convey readily correctable issues to the applicant in a timely manner as they are identified with the expectation that they should be addressed quickly."*

    Recommendation: PhRMA suggests deleting the word *"routinely"*.

66. Lines 525 – 528: *"Though inquiries from the applicant to the FDA during the application receipt process are generally unnecessary, the applicant is likely to receive communications from the FDA and should respond accordingly."*

    Recommendation: PhRMA suggests allowing communication for clarifying questions regarding input from consultations, etc. This transparency on the FDA's part will allow applicants to inquire less frequently of the outcome of the consultations, and therefore increase efficiency.

67. Lines 538-539: *"We encourage communication with the applicant throughout the review process through secure e-mail,…."*

    Recommendation: PhRMA suggests revising the text to read as follows: "*We encourage communication between the applicant and FDA….*" Additionally, is a special arrangement required with the reviewing Division to have *"secure e-mail"*?

68. Line 552: *"… the required information and format…"*

    Recommendation: PhRMA suggests revising the text to read as follows: *"…the required information*" since the CFR currently does not specify CTD format and the guidance should reflect current expectations.

69. Lines 579 - 581: *"In many instances, it may be useful for each discipline to document the filing process decisions in a brief filing review."*

    Recommendation: The language, *"In many instances, it may be useful…"* suggests that FDA does not consider it to be a good review management principle to routinely document

filing process decisions in this way. Therefore, some detail on when GRMPs would call for brief filing reviews should be provided. The guidance should also clarify whether such documentation is application specific (that is, whether all disciplines should write brief filing reviews on certain applications) or discipline specific (written reviews are only recommended for disciplines whose conclusions may result in a refusal to file decision.)

70. Lines 586 - 589: *"The filing meeting is often held approximately 45 days after receipt of a standard review application, but in some cases, the review team should consider compressing the receipt/filing process."*

Recommendation: The general nature of this statement makes it difficult to discern what FDA considers "good review management" to be. Would it be preferable if *all* filing meetings were scheduled earlier than 45 days from receipt? If not, what makes some applications candidates for an earlier meeting? Should filing meetings for all priority applications be scheduled early and, if so, what time-frame, based on experience, could be recommended? The value of the document would be improved by providing more specific recommendations to establish the presumed "gold standard" for the various activities discussed thereby providing review teams with a yardstick against which to measure their progress.

71. Line 601: *"Issues that potentially merit advisory committee input"*

Recommendation: The guidance should encourage the agency to communicate this decision to the applicant at the time the decision is made (Filing meeting). This will allow the applicant to prepare for the advisory meeting and will reduce redundancy of the presentations, since the applicant can share their presentations with the agency in time.

72. Lines 609 – 612: *"Although communication with the applicant regarding application content is recommended prior to the filing meeting (e.g., to correct minor application deficiencies), additional issues may nevertheless be identified during the filing meeting."*

Recommendation: PhRMA recommends that communication be consistent with Line 533.

73. Lines 615 – 622: *"If the deficiencies appear to be readily correctable, the division should promptly notify the applicant of the deficiencies and establish a date by which the applicant must satisfactorily respond to avoid a refuse-to-file decision. If the reviewers believe that the deficiencies are not readily correctable by the applicant, or if the applicant fails to respond satisfactorily to notification of refuse-to-file issues, the specific refuse-to-file deficiencies should be conveyed to the applicant in a letter signed by the review division director (see next section)."*

Recommendation: PhRMA suggests revising the text to read as follows: *"If the deficiencies appear to be readily correctable, the division should promptly notify the applicant of the deficiencies and recommend an appropriate response to correct the deficiencies. If the reviewers, after consulting with the applicant, believe that the deficiencies are not readily correctable by the applicant, the division should discuss the issues with the applicant prior to making a final determination. If the reviewers then conclude that the deficiencies are not readily correctable or the applicant fails to respond*

satisfactorily to notification of refuse-to-file issues, the specific refuse-to-file deficiencies should be conveyed to the applicant in a letter signed by the review division director (see next section)."

FDA should not independently determine that a given deficiency is not readily correctable, without first discussing the issue with the applicant and learning the timing for correction of the deficiencies. The applicant and the review team should together define those issues that are readily correctable. It may appear that an issue is significant to the review team, when the applicant is actually capable of quickly resolving the deficiency.

74. Lines 624 – 625: *"Requests for additional information from the applicant and filing review issues raised during the filing meeting should be communicated to the applicant."*

Recommendation: PhRMA suggests adding the following text: *"Responses to information requests prior to filing are considered part of the initial submission and should be reviewed during the initial review cycle"* to clarify that the initial application as filed, including any amendments solicited during the filing assessment, is complete and not considered amended and hence is reviewable during the first cycle.

75. Lines 646 – 648: "*Various types of application deficiencies may be identified during the filing process, and the applicant should be aware of the available responses to each and the potential effect of those responses on the FDA review process."*

Recommendation: PhRMA suggests the following text: "*Various types of application deficiencies may be identified during the filing process, and the applicant should have been advised by FDA of the available responses…"*

76. Lines 648 - 652: *"Specific information requests from the FDA should be addressed expediently to facilitate the review. The applicant should be aware that amendments containing responses to filing review issues identified by the FDA and communicated according to the PDUFA goals may or may not be reviewed by the FDA during the first review cycle."*

Recommendation: While there is emphasis on early identification and communication of application deficiencies in the discussion of the receipt the filing review processes, the notion that it may be a good review management principle for FDA to not even review the amendments expediently submitted by the applicant in response to such early communications requires, at least, some explanation.

PhRMA suggests adding the following text: *"FDA will notify the applicant of this decision in the information request letter."* In the spirit of transparency, in the IR letter FDA should indicate to the applicant whether a complete response will be included in the first review cycle. It may be appropriate for FDA to specify a date by which a complete response will be included in the first review cycle. This information will assist the applicant in appropriately prioritizing its response.

77. Line 678 - Subsection IV. D. - *Review Planning*

Recommendation: The description of the review planning process is vague and lacking in detail. This section would be enhanced by providing further detail around the following:

- Timing - while the draft guidance indicates that *"In most cases, the initial review planning activity should be combined with the filing meeting..."* the timing for completing the review plan is not discussed further.
- Responsibility - who is responsible for the planning (Division Director? Deputy Director? RPM? Supervisory RPM)?
- Workload and staffing in the review division and consultant divisions - how does the person responsible for review planning assess these factors? Are workload and staffing statistics routinely available to review teams.
- Is it expected, as a GRMP, that a written review management plan (for example, in the form of a project management timeline) will be prepared? If so, who is responsible for preparing it and updating it as the review progresses? Is it shared with Division management so that progress against the plan can be evaluated?

78. Line 682: *"Planning for the entire review process should occur early in the review cycle...."*

Recommendation: PhRMA suggests defining the term "early" which will clarify timelines.

79. Lines 694 – 700: FDA Planning

Recommendation: PhRMA suggests incorporating the following activities in this planning process which will allow for a more efficient system and sponsors will inquire less frequently:

- Determining additional resource needs
- Planning meetings with applicant to give status reports and answer questions
- FDA consultants
- Labeling & marketing discussions
- DSI
- Field Audits

80. Lines 710 - 714: *"An applicant can best support the planning process by providing accurate projected timelines for response to information requests and submission of expected amendments (e.g., safety updates). Failure to meet projected timelines has a systemic impact on the FDA review process, reaching beyond the intended submission's discipline-specific material."*

Recommendation: It would be beneficial to expand on this statement that failure by the applicant to meet projected timelines has a systemic impact on the review process reaching beyond the intended submission's discipline-specific material. It is also unclear how other areas are impacted.

81. Lines 718 - 719: *"In planning for the review process, the FDA is committed to managing efficiently the communication of concerns to the applicant and the timing of the applicant responses."*

Recommendation: There is a concern regarding FDA's strategy to "manage efficiently the communication of concerns to the applicant and the timing of the applicant responses."

This statement suggests that the review division may delay or defer the communication of concerns to sponsors in order to control the timing of applicant responses. PhRMA suggests that this sentence be revised to include language confirming that FDA will communicate deficiencies to the applicant as early as possible after they are identified to ensure consideration of the timeframe in which the applicant will need to respond.

82. Lines 718-722: D.3. Communication between FDA and Applicant

Recommendation: PhRMA members have had very positive experiences working with an FDA division that shared an abbreviated timeline with the applicant. We would highly recommend consideration of implementing such a tool for planning and communication purposes between FDA and the applicant. At a minimum, this timeline should consist of actual or estimated dates for the 45-day review meeting, the filing date, the 4-month safety update, the mid-cycle review meeting, an Advisory meeting if expected, the final safety update, and the action date. Any planned and agreed upon application amendments could be added to this timeline as well.

83. Lines 720 – 722: *"The applicant should not expect to be apprised of all interim timelines for internal FDA processes, but will be involved by the FDA in planning activities that clearly require applicant input, such as an advisory committee meeting."*

Recommendation: PhRMA suggests revising the text to read as follows: *"The applicant should not expect to be apprised of all interim timelines for internal FDA processes, but will be involved by the FDA in planning activities that clearly require applicant input, such as an advisory committee meeting, information requests, discipline review letters and inspections. An overall high-level timeline should be supplied to the applicant including the previously mentioned milestones and any changes to the timeline should be communicated."*

PhRMA suggests that FDA develop a "model review time line" to allow for clarity in the process. We also strongly suggest more specific guidance providing that Medical Reviewers should make a judgment about the need to go to advisory committee at the time of the filing meeting, and that this recommendation be relayed to the applicant when the application is filed.

84. Lines 731 – 734: "*For optimal review efficiency, primary and secondary reviewers (e.g., team leaders, branch chiefs, and first-line supervisors) should observe the timelines and interim goals for review progress established during the planning process. Primary and secondary reviewers are responsible for managing their individual workloads to accommodate the schedules of multiple projects."*

Recommendation: While we understand the need for flexibility in managing workload overall, interim goals should be relayed to the sponsor.

85. Lines 740 – 742: *"Any changes to the planned timeline for the review should be communicated among the entire review team and discussed with the signatory authority for the application."*

Recommendation: PhRMA suggests revising the text to read as follows: *"Any changes to the planned timeline for the review should be communicated among the entire review team and discussed with the signatory authority for the application. The applicant should be notified."*

86. Lines 763 – 764: "*The secondary reviewer finalizes the primary reviews from each discipline with secondary sign-off.*"

Recommendation: PhRMA suggests revising the text to read: "*For each discipline, the secondary reviewer finalizes and approves the primary reviews.*" We also recommend defining the roles of the review teams for clarity. Additionally, generic timelines should be developed for when the primary review will be targeted for completion.

87. Lines 772 – 779 and 811 – 813: *"It is generally expected that secondary reviewers will write their own brief review… In some cases (e.g., no disagreement between the primary and secondary reviewers and a well-written executive summary by the primary reviewer), it may not be necessary for the secondary reviewer to write a separate review."*

Recommendation: The written opinion of the secondary reviewer should be required, even if this is a simple concurrence with the primary reviewer. This will provide additional clarity of process.

88. Lines 783 – 785: "*If a primary reviewer and team leader are unable to reach agreement on one or more important finding, conclusion, or recommendation, the primary reviewer should proceed by entering his or her signed review into the division archive.*"

Recommendation: When unresolved differences persist between primary and secondary reviewers, we suggest that the guidance emphasize that the content of the review must remain focused on a scientific assessment of the data. Reviewers should be reminded that editorial comments, unsubstantiated opinions, or speculative statements should be avoided.

89. Lines 809 – 811: "*The division director should also describe how input from the an advisory committee, if held, was factored into the action.*"

Recommendation: For transparency of the process, we recommend that the sponsor be informed of the rationale.

90. Line 820: Interdisciplinary Communication

Recommendation: There should be specific mention of the need to be diligent in obtaining any necessary expert opinions from outside the division, since these may have important implications for the conduct of the review and/or approval, yet may be procedurally more difficult to obtain and integrate with the reviews conducted by staff within the division There is no specific mention of interdivisional consultations in this section. Concerns have been expressed about the need to integrate the reviews of different disciplines within a single division.

91. Lines 834 – 837: "*Any multidisciplinary issue that may affect the review timeline established during the planning process should be communicated to the entire team, including the team leaders and the review division director, as soon as it is identified.*"

    Recommendation: PhRMA recommends that the sponsor should also be included in this communication.

92. Lines 859 – 862: *"The review division director does not generally review DR letters before they are issued, and any deficiencies or requests for additional data or analyses contained in a DR letter do not represent final Agency action on the application."*

    Recommendation: PhRMA request clarification on the following: (a) what if a DR letter is issued and, at a later date, the Division Director disagrees with the content of the letter? (b) When does the Division Director not review DR letters?

93. Lines 874 – 876: *"In such cases, it is generally most efficient to include any substantive deficiencies identified by the discipline review in the action letter for the application."*

    Recommendation: Substantive deficiencies should be communicated to the applicant regardless of the PDUFA goal date. If possible, substantive deficiencies should not be withheld from the applicant, as this will ultimately delay the review and approval. This philosophy is also discussed on line 1339.

94. Lines 876 - 885: *"A decision regarding whether to send the DR letter in such cases* [when the review is completed only shortly before (1 or 2 weeks) the PDUFA goal date or shortly before planned comprehensive action prior to the PDUFA goal date] *should be discussed with the review division director. The review division director's decision should be based on an analysis of the overall status of the application review and the most efficient way to complete the review within the PDUFA goals. Consideration should be given to the seriousness of the identified deficiencies and the expected time required for the applicant to respond satisfactorily, knowledge of any other serious deficiencies that might prevent approval of the application on the first cycle, competing division workload priorities, and division resource allocation."*

    If GRMPs are being followed, the completion of a review only 1 or 2 weeks before the PDUFA goal date or shortly before *planned* comprehensive action should not occur. Such an occurrence would, presumably, be prevented by the regularly scheduled team meetings to discuss the progress of the review with respect to the time line established at its onset. Secondly, the language describing the basis for the review division director's decision focuses only on completion within PDUFA goals. The language describing factors to be considered fails to mention the seriousness of the disease for which the product is intended or its potential to meet an unmet need. Thus, under the scenario described, it would never be considered a GRMP to conclude that the importance of early access to the product could supersede acting within the goal date, even though PDUFA goals do not demand that FDA complete reviews on 100% of its workload within the specified dates.

    Recommendation: (1) It is assumed that, as review divisions implement and adhere to GRMPs as described in the draft guidance, the situation where a review is not completed

until almost 2 weeks prior to a planned action date should be rare. Given the definition of a discipline review (DR) letter, its content is virtually final at the time the review is finished since the content of the letter is not reviewed or agreed upon by the Division Director and its content is not to be taken by the applicant as final. Therefore, any inefficiency in issuing the letter should be minor in nature. We encourage the agency to issue DR letters in all but the most unusual of circumstances.

(2) It is recommended that the GRMP guidance include language that, at least, provides for the possibility of a review division opting to miss a first cycle goal date for an important product intended to treat a serious or life-threatening disease when the Division Director, perhaps with authorization from the Office or Center level, determines that the product can be approved and made available more quickly than if it undergoes a 2nd cycle review.

(3) It is recommended that "expected time" for the applicant to respond satisfactorily, competing division workload priorities, and division resource allocation should not be factors considered by the review division in determining whether or not to send a DR letter. "Workload priorities" and "division resource allocation" should be specifically cited as factors not to be considered. These factors encourage favoring one application over another on the basis of factors unrelated to the content of the application itself, thereby compromising the "level playing field" that the PDUFA goals established.

(4) Lines 881-885: PhRMA suggest revising the text to read as follows: "Consideration should be given to the seriousness of the identified deficiencies and timing of the response. The expected time required for the applicant to respond satisfactorily should be discussed directly with the applicant. Also knowledge of any other serious deficiencies that might prevent approval of the application on the first cycle, competing division workload priorities, and division resource allocation should be considered and discussed." The applicant should be involved in the discussions to facilitate the decision making process based on the information known only by the applicant.

95. Lines 887 - 890: *"The review division will decide whether it is appropriate to review amendments submitted during the first-cycle review or defer review to a subsequent review cycle based on the divisions workload and priorities and the review timeline with respect to the nature of the deficiencies."* And...

Lines 899 - 902: *"The division's workload and priorities, and the review timeline and nature of the deficiencies addressed in the amendment also are critical to deciding whether to review them during the first cycle."*

Recommendation: PhRMA suggests adding the following sentence before Line 887: *"The review division will review all information as agreed to in pre-submission meetings. The review division should clearly communicate the review plan and timing with the applicant."* It is important that the applicant know the review plans and any changes in the agreements or review schedule must be communicated to the applicant.

Additionally, it is recommended that division workload and division priorities should not be factors included in the decision to review amendments submitted during the first-cycle review.

96. Lines 912 - 919: *Under PDUFA, major amendments submitted during the last three months of the first-cycle review might lead to a three-month extension of the review clock. The review division retains the authority to determine whether to extend the review clock in response to such amendments. In making this decision, the review division should consider the contents of the amendment, the status of each discipline's review for the application, the division's workload and staffing, and the likelihood that review of the major amendment could lead to approval of the application during the first-cycle review.*

    Recommendation: Identifying the parameters of a "major amendment" would clarify expectations for the applicant.

97. Lines 930 – 933: "*Applicants can best contribute to efficient first-cycle review by initially providing a complete application, submitting planned amendments (e.g., safety and stability updates) on a timely basis, and quickly and completely responding to IR letters and other requests for information.*"

    Recommendation: PhRMA recommends that the final guidance should state that a complete application would include fulfilling any commitments identified during development.

98. Page 22. Footnote 11. CBER SOPP

    Recommendation: PhRMA recommends including CDER MAPP if applicable since this guidance reflects both Centers.

99. Lines 953 - 958: *"Requests for meetings primarily focused on status updates generally are not an efficient use of the review division's limited time and resources and may actually slow the review process because of the need for preparation. Such meeting requests ordinarily will be denied. More efficient means of providing the applicant with an update on the application review status should be used (e.g., a telephone call between the RPM and the applicant.)"*

    Recommendation: We agree that "status update" meetings are generally not efficient for the agency or for the applicant. However, we recommend the Centers consider implementing a process to assure that the RPM has access to up-to-date information about the status of applications and clear authority to convey information to the applicant so that telephone calls between the RPM and applicant are routinely effective in communicating the information to the applicant (see related comment on Lines 1323 - 1327).

    PhRMA also suggests revising the text to read as follows: "*More efficient means of providing the applicant with an update on the application review status should be made following each regular review team meeting.*"

100. Lines 958 - 959: *"Routine conveyance by the FDA of the interim review process timelines and speculative action dates is discouraged."*

Recommendation: It is recommended that this position be reconsidered since it contradicts with Lines 956 - 958. Conveying the projected timeline to the applicant and encouraging the RPM to share updates to the timeline with the applicant should the applicant telephone to inquire about the review status would provide useful information to the applicant and is likely to reduce the volume of status inquiries. As noted on lines 24-26, a key aspect of GRMPs is "their emphasis on effective communication between the Agency and applicants throughout the drug and biologic product development and review process." Efforts to censor or control such communication should be discouraged.

101. Lines 961: F. Advisory Committee Meetings and Lines 966-968: "*The decision regarding whether to present an application to an Advisory Committee (AC) generally is made by the review division in consultation with the office director early in the first-cycle review process.*"

Recommendation: Although the GRMP draft indicates that the decision regarding whether an Advisory Committee meeting is going to be necessary is made early in the first-cycle review process, we encourage the FDA to communicate this information to the sponsor ASAP, e.g. pre-NDA meeting. The resources needed for the sponsor to prepare their AC presentation and to support any FDA requests related to the Division's AC presentation are significant and can impact the ability to respond quickly to review questions or other requests. The earlier the notice of a Committee meeting (regardless of whether a date is identified) is conveyed to the sponsor, the more effective the resource planning process can be.

The Agency should also encourage sharing of slides, with an opportunity for open discussion of issues. This would minimize discussion between FDA and the applicant and allow the meeting to stay focused on the feedback from the committee. The FDA should request the applicant's feedback on issues raised by the advisory committee.

102. Lines 991 - 993: (Planning for an Advisory Committee) - *"The applicant should be notified when it is determined that an AC meeting will be needed and should be consulted during the scheduling process."*

Recommendation: Under planning for Advisory Committee, there should be a specific timeline under which the RPM would advise the applicant of the likelihood of an Advisory Committee meeting. Generally, the applicant would need at least three months to prepare for an Advisory Committee meeting. Therefore, this should be discussed within the Agency during the 45 day meeting and a decision should be reached at that point and communicated to the applicant. The decision could be based on the likelihood of having an Advisory Committee meeting.

103. Lines 1019 – 1021: "*However, the final questions should be provided to the committee and applicant as far in advance of the actual meeting as feasible.*"

Recommendation: PhRMA suggests revising the text to read: "*However, the final questions should be provided to the committee and applicant as far in advance, e.g. 48 hours, ...*"

104. Lines 1030 – 1032: *"A neutral presentation that invites all AC viewpoints does not preclude the division from highlighting concerns about the application or presenting preliminary conclusions regarding the data contained in the application."*

Recommendation: PhRMA suggests replacing the term "neutral" with "balanced".

105. Lines 1035 –1036: *"This goal can best be accomplished if the review division and the applicant work together and share information and presentations in advance of the meeting."*

Recommendation: PhRMA agrees that AC meetings are most likely to be successful if there is a partnership and collaboration with the Agency. We also suggest whenever possible to have pre-AC meetings to review the presentations and information.

106. Lines 1082-1083: *"...as far in advance of the meeting as feasible to facilitate meeting efficiency...."*

Recommendation: PhRMA suggests replacing *"as far in advance"* with *"reasonably in advance" (e.g. 1 month).*

107. Line 1086: *"The review division generally will share its presentation with the applicant in advance of the AC meeting."*

Recommendation: PhRMA suggests the following:

- Deleting the word *"generally"* since it should be standard practice to share presentations for AC meetings.
- Replacing *"in advance"* with *"reasonably in advance" (e.g. 1 month).*

108. Lines 1107 – 1109: *"This goal can best be achieved when both the applicant and the division adhere to the timelines for submission of background packages to the committee and share their presentations with one another in advance of the meeting."*

Recommendation: PhRMA recommends the term "in advance" be replaced with "reasonably in advance".

WRAP-UP AND LABELING

109. Lines 1123 – 1124: *"...this meeting can be used to identify the requisite parameters for the subsequent labeling negotiation."*

Recommendation: PhRMA suggests that *"requisite parameters"* be defined and clarified.

110. Lines 1130 – 1131: *"The planning process should also anticipate communication events with the applicant for labeling negotiation."*

Recommendation: PhRMA suggests that *"communication events"* be defined and clarified and recommends adding the following text at the end of the sentence: *"which should occur 4 weeks before the review date."*

111. Lines 1283 – 1286: "*If the application is not expected to be approved on the first cycle, the draft action letter should list all the deficiencies identified by the reviewers that must be remedied prior to approval and should also specify how the applicant is expected to respond to each deficiency.*"

Recommendation: PhRMA suggests revising the text to read as follows: "*If the application is not expected to be approved on the first cycle, the draft action letter should list all the deficiencies identified by the reviewers that must be remedied prior to approval and should list the specific information on how to correct the deficiencies.*"

112. Lines 1321 – 1323: "*Based on the nature of communications between the applicant and the review division throughout the review process (e.g., IR letters, DR letters, labeling negotiations), it should be reasonably clear to the applicant whether the application may be headed toward approval or whether another review cycle will be needed to address the Agency's concerns.*"

Recommendation: PhRMA recommends moving this statement under the "FDA Focus" section (Line 1209) and suggests the following text revision, "*...(e.g., IR letter, DR letters, labeling negotiations), the FDA should make it clear to the applicant whether the application may be headed toward approval or whether another review cycle will be needed to address the Agency's concerns.*"

113. Lines 1131 – 1133: "*The negotiation should be implemented well in advance of the final action goal date and should not impede timely completion of the first-cycle review.*"

Recommendation: It is suggested that a phrase be added for CMA allowance of early label negotiations.

114. Lines 1142 – 1143: "*Early communication of potential labeling issues....*"

Recommendation: Early communication of labeling issues does not usually occur. They are typically discussed in an intense frenzy just prior to the Action Due date. We encourage a change in usual practice in this regard and suggest revising the text to read: "*Early communication, at least two weeks prior to the action date, of labeling issues....*" General terms, such as early, need a clear definition to allow the applicant and FDA a clear understanding of the expectations.

115. Lines 1158 - 1162: "*Applicants are discouraged from printing labels for commercial distribution prior to receipt of an approval letter, because the label is not considered approved by the FDA until then. Labels printed in advance of the actual receipt of an approval letter can contain differences from the final approved label and may have been destroyed.*"

Recommendation: FDA should consider whether it means "labeling" instead of "label" in the above sentence based on the definitions in the FD&C Act.[4] The same consideration should be given to the use of the word "label" on line 1169.

Additionally, it is recognized that negotiation of the package insert language is an activity that perforce needs to occur after the full application review is complete and therefore cannot be considered final until the approval letter is issued. However, it would seem that container labeling could be reviewed earlier in the application review cycle, so that any changes requested by the reviewers could be addressed and the labeling finalized. Since manufacture of launch supplies cannot occur until the immediate container labels are final printed for application during manufacture, final approval of the container labels becomes a rate-limiting step. By moving the review of the container labels earlier in the review and indicating when they are considered acceptable to FDA, sponsors could prepare supplies for launch and await the final package insert with the approval letter.

116. Lines 1164 – 1179: Communication between FDA and Applicant

Recommendation: It would be important to emphasize that this dialogue should begin earlier in the process. The concepts in Lines 1142-1147 should be restated here. Sponsors are sometimes put in a difficult position of accepting sub-optimal labeling in order to gain approval by the PDUFA goal date.

117. Lines 1169 – 1171: *"This approach should improve the efficiency of communication by decreasing the number of back-and-forth negotiations between the division and the applicant."*

Recommendation: PhRMA suggests revising the text to read as follows: "*Web conferencing or direct discussion of labeling is encouraged to minimize the delays associated with faxing proposals back and forth."* A practice commonly used is to fax proposed language and counter-proposals back and forth between FDA and the applicant. Direct discussion and resolution through means such as online conferencing would be more efficient.

118. Line 1179: 21 USC 352

Recommendation: It is recommended that this acronym be defined in Appendix A.

119. Line 1181 – H. Action

Recommendation: It would be helpful to include language here to indicate that the FDA should inform the sponsor (within some specified timeframe) if the agency believes that the application is not approvable. Typically the sponsor knows this; however, there have been

[4] See FD&C Act, Section 201(k), "The term 'label' means a display of written, printed, or graphic matter upon the immediate container of any article..."; and Section 201(m), "The term 'labeling' means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."

times where this has come as an unfortunate surprise to the applicant. Including this as a step in the process will help to lesson the chance of this happening.

Following receipt of an action letter, the applicant may wish to hold a brief telephone conference with the principle signatory in the office and/or review division to ensure full understanding of the decision. We recommend that the results of the action letter (especially if non approval or approvable letter) should be discussed prior to the action letter.

Additionally, it would be helpful to applicants if the processes for NDAs and BLAs were harmonized.

120. Lines 1185 - 1188: *"Agency actions at the end of the application review can be to approve the application for marketing...or to provide the applicant with a comprehensive list of deficiencies...."*

Recommendation: It is recommended that the phrase "*comprehensive list of deficiencies*" in the above sentence be replaced with the phrase "*complete list of deficiencies.*"

121. Lines 1200 – 1207: *"or BLAs, an application that is not approved receives a complete response letter listing all the deficiencies to be corrected to FDA's satisfaction before the application can be approved. Under the PDUFA goals, the FDA was directed to eliminate the use of approvable and nonapprovable letters and implement use of complete response letters. The FDA is working to amend its regulations since these letters are currently defined in the Code of Federal Regulations for new drug applications."*

Recommendation: Clarification is requested on the following - Will biotech products that have just been transferred from CBER to CDER now be subject to Approvable and Not Approvable letters?

122. Line 1228: *"...weeks before the PDUFA goal data...."*

Recommendation: The word "*data*" should be changed to "*date.*"

123. Lines 1273 - 1275: *"If approval is anticipated, the draft action letter should specify all the conditions of approval, including labeling text, any postmarketing study commitments, and any restrictions on distribution of the product when warranted."*

Recommendations: Restrictions on distribution would, presumably, be a feature of a risk management plan. Unless it is FDA's intent only to include information on restrictions on distribution, the guidance might instead recommend including a summary of any risk management plan agreed upon by the applicant.

124. Lines 1283 - 1286: *"If the application is not expected to be approved on the first cycle, the draft action letter should list all the deficiencies identified by the reviewers that must be remedied prior to approval and should also specify how the applicant is expected to respond to each deficiency."*

Recommendation: Further clarification should be provided on the point that the action letter should specify how the applicant is expected to respond to each deficiency.

125. Lines 1288 - 1296: *"The draft letter should be circulated to all members of the review team and their team leaders and supervisors for review and concurrence before being forwarded along with the action package to the signatory authority. Depending on the review and decisions made...."*

Recommendation: It may be helpful to provide some timing parameters to improve the efficiency of circulation of the final review. Is there some range of time that is considered a GRMP within which a reviewer or team leader is expected to review the draft letter and move it forward? This would also help the RMP to plan finalization of the letter for signature.

126. Subsection beginning at line 1305: *"e. Process for Conveyance of Action"*

Recommendation: This subsection notes that the signed letter is archived in division files and a copy is sent to the applicant via facsimile. The RPM calls the applicant to document that it was received and documents the fact in the action package. It is not clear whether or not the original letter is actually mailed to the applicant.

127. Lines 1309: *"...and a copy sent to the applicant by facsimile."*

Recommendation: PhRMA suggests revising the text to read as follows: *"...and a copy sent to the applicant by facsimile, or scanned and sent through secure e-mail."* Secure e-mail should be an acceptable means of communication when possible.

128. Lines 1321 - 1323: *"...it should be reasonably clear to the applicant whether the application may be headed toward approval or whether another review cycle will be needed to address the Agency's concerns."*

Recommendation: PhRMA suggests revising the text to read as follows: "*...it should be clearly communicated to the applicant whether the application is headed toward approval or whether another review cycle will be needed to address the Agency's concerns.*" Good communication is an important part of the review process, and the applicant should not need to assume approval will or will not occur.

129. Lines 1323 - 1327: *"It is generally not an efficient use of Agency resources during this final critical period to be responding to frequent and redundant inquiries from the applicant. There should be only one point of contact, the RPM, between the applicant and the review division to ensure consistency of communication and to avoid misunderstandings."*

Recommendation: We agree that frequent and redundant inquiries are not an efficient use of the resources of the agency or the applicant. We further agree that the RPM should be the one point of contact. Frequency and redundancy of inquiries, however, may be spawned, in part, by the unsatisfactory nature of the communication. While we recognize that there are limits to the information that can be made available, we recommend the Centers consider implementing a process to assure that the RPM has up-to-date

information during the critical end-of-review process and is clear on what information can be shared with the applicant. This would help to assure that communications between the RPM and applicant are routinely effective in communicating the information to the applicant and would largely eliminate inquiries that are considered redundant by the agency (See also comment at 29 above).

130. Line 1333: *"Communication between FDA and Industry"*

Recommendation: PhRMA suggests changing *"Industry"* to *"Applicant,"* for consistency with other sections.

131. Line 1352: *"...(e.g., RTF, ..."*

Recommendation: It is recommended that "RTF" be listed in Appendix A, "Glossary of Acronyms."

132. Lines 1369 - 1372: *"Once the signatory authority for the application makes his or her decision regarding official regulatory action for the application, the decision should be communicated in writing to the applicant as an official written regulatory action (e.g., refuse-to-file, approval, nonapproval, complete response) in a timely and appropriate manner."*

Recommendation: PhRMA believes it would be useful to review division management and RPMs to add a recommended time frame that Center management considers to be within GRMPs. Otherwise, the term "timely" carries little meaning. We also suggest revising *"(e.g., refuse-to-file, approval, nonapproval, complete response"* to *"...approval, complete response)"* since the terminology is inconsistent with that used on Line 1205. In the final guidance, we also suggest a statement that the official regulatory action for the application should only be communicated to the individual specified by the applicant; generally, the signatory of the original application.

133. Lines 1379 - 1382: *"Following receipt of an action letter, the applicant may wish to hold a brief telephone conference with the principal signatory in the office and/or review division to ensure full understanding of the decision."*

Recommendation: The guidance should stipulate whether the request for this teleconference must follow the standard meeting management goals with respect to the timing of the meeting and the need for submission of background material.

134. Lines 1403 – 1407: *"An end of review conference, described in 21 CFR 314.102(d), provides the applicant with the opportunity to meet with the FDA reviewing officials following issuance of an approvable, nonapprovable or complete response letter. This meeting is recommended if the applicant has questions regarding the identified deficiencies and to support further development and submission planning."*

Recommendation: As 314.102 (d) is applicable to drugs and not to biologics, is there a similar mechanism for biologics (non-biotech) regulated by CBER to conduct an "end of review" meeting?

APPENDIX B: REFERENCED GUIDANCES, MAPPS AND SOPPS

135. Appendix B: References

Recommendation: PhRMA suggests hyperlinking to specific documents wherever possible.