BIO

BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 03D-0317, Federal Register: July 28, 2003 (Volume 68, Number 144, Page 44345-44346)

Dear Dr. Jenkins and Dr. Yetter:

The following comments are provided by the Biotechnology Industry Organization (BIO) on the Food and Drug Administration's (FDA) draft guidance dated July 2003 on *Good Review Management Principles for PDUFA Products*. BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the FDA's draft guidance on Good Review Management Principles (GRMPs).

In the Commissioner's *Improving Innovation in Medical Technology: Beyond 2002,* a significant review was undertaken documenting that nearly half of all new drug applications filed with FDA's reviewing divisions fail to reach approval during the agreed upon Prescription Drug User Fee Act (PDUFA) review period. Although FDA is meeting its obligations to review applications within the established PDUFA time frames, 6 months for priority applications and 10 months for standard applications, the potential exists to improve upon the percentage of applications approved within the first review cycle. As stated by Dr. McClellan when announcing the launch of FDA's initiatives for 2003, "FDA...can take steps to help by making the drug development and our review processes more efficient and effective." We believe this can be accomplished by adopting best practices for management of the regulatory review process, thereby gaining efficiency in the conduct of the review process. Improving the efficiency of the review process would result in faster availability of safe and effective products for the patients who need them.

BIO believes the proposed *Good Review Management Principles for PDUFA Products* is a significant step for FDA toward establishing best practices and improving the efficiency of the review process. Coupled with the new PDUFA goal for early notification of issues identified during the filing review period, plus the substantial increase in resources FDA will receive from

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increased user fee revenues under PDUFA III, the FDA will be better positioned in the future to complete the review and take final action without subjecting applications to multiple review cycles. We also acknowledge that realizing the full potential of this initiative is not solely FDA's responsibility; achieving the desired improvements depends also on applicants submitting complete applications and timely responses to inquiries from FDA review personnel as well as the quality of the data.

Despite our strong belief in the merits of this initiative, BIO does have a number of concerns with certain aspects of the July 2003 draft guidance. Our main areas for concern fall into the following general categories:

- We believe the draft is too vague and subjective in many areas, with overuse of non-specific terms such as "generally recommended" and "as soon as possible". Greater specificity is needed, especially regarding the timing of certain agency activities during the review process (for example, discussion of labeling with the applicant).

- We recommend adding greater emphasis on improving transparency of the review process. Increasing transparency by communicating with the applicant about key review milestones would help the applicant plan for interactions that can be anticipated. Examples include timing for receipt of comments on draft labeling, and for completion of discipline reviews. This would enable the applicant to have personnel on alert who have the appropriate expertise to address review comments, thereby facilitating the timeliness of the applicant's response.

- We recommend adding text to cover communications between the agency and applicant regarding post-approval commitments. This is a critical area that can involve a very significant commitment of industry and agency resources, and we believe time should be planned in the review process to ensure there are meaningful interactions regarding the objectives, scope and feasibility of any proposed studies. We have proposed the addition of text to address this important area (see comments on pages 10 and 11, under *Wrap-Up and Labeling*).

- We believe the draft guidance is unnecessarily restrictive regarding the submission of amendments to an application and their review during the first cycle. The overwhelming majority of amendments are submitted in direct response to FDA requests for additional information or clarification. Earlier communication of such requests in accordance with GRMPs will ordinarily result in receipt of applicant responses earlier in the first review cycle, allowing FDA a greater amount of time to complete its review of the application before or by the PDUFA goal date.

- While the draft guidance describes the need for an applicant to provide FDA with a complete application upon initial submission, it does not consider programs such as Fast-Track or the Continuous Marketing Application pilots as examples where flexibility in the approach to review and provide feedback on "complete" reviewable units is an option. We recommend that FDA include these options in the guidance.

- The draft guidance does not address means of improving the review process for complex products such as combination products that may require multiple consultancies involving different review divisions or Centers. While the Office of Combination Products is helpful for determining the responsible reviewing Center, review of combination products would also benefit from having an oversight or coordinating body with authority to ensure that the review of combination products are effectively coordinated. This would ideally be established within the Office of Combination Products so as not to provide for a more bureaucratic process.

While BIO recognizes and appreciates the considerable time and effort expended by FDA personnel to prepare the draft guidance, we are concerned that the performance goals envisioned under PDUFA III will not be realized unless the issues noted above are addressed in the final guidance. In addition, in order to maximize the assimilation of GRMPs into existing review processes we suggest that training on, and adherence to, GRMPs should be a component of the performance objectives and evaluation system for review personnel. Our detailed comments are provided below, organized according to the section headings contained in the draft guidance.

Specific Comments

Section II - Background section

- Lines 56-57: We believe the sentence, "Therefore, many GRMPs are currently in practice" does not contribute to the overall purpose of the document. While some are undoubtedly practiced, consistency is generally lacking between review divisions and centers. Indeed, if many GRMPs were truly routinely practiced, there would not have been any motivation to adopt this as a PDUFA III performance goal. We therefore recommend that this sentence be deleted.

- Lines 62-63: The sentence, "*For review staff and managers to adhere consistently to these review principles, the FDA is dependent on the availability of adequate resources...*" seems to ignore the very substantial increase in user fee funding the agency will receive under PDUFA III. BIO believes that the significant resources funded by user fee revenues in previous years under PDUFA I and II, in addition to the increased revenues to be received under PDUFA III provides the full resource level that FDA needs to meet all of its PDUFA commitments. Under PDUFA III FDA agreed to a commitment to conduct a comprehensive process review and analysis within CDER and CBER covering information utilization, review management and activity cost. The results of this analysis should provide more precise data for projecting FDA resource needs and utilization of technology.

Section III - Overall Principles

- Lines 93-101: BIO generally agrees with the concepts described in this paragraph, i.e., for products that otherwise meet the standards for approval a well-managed review process should result in issuance of an approval letter on or before the PDUFA goal date, thereby eliminating additional unnecessary and inefficient review cycles. It is also

noteworthy that the well-managed process allows for "finalization of the labeling and other regulatory issues (e.g., negotiation of post marketing commitments)." However, this latter point regarding post marketing commitments is not discussed anywhere else in the draft guidance. BIO believes this is a very important aspect of the review process that merits greater attention, and we have proposed text later in these comments to address this point (*see comments on section IV.G., Wrap-Up and Labeling*).

Lines 103-108: BIO agrees that timely notification of deficiencies is a key principle of a well-managed first-cycle review process. The sentence beginning on line 105 reads, "*Often, timely notification of correctable deficiencies allows the applicant to begin the additional studies or corrective actions needed to address the deficiencies, reduce the number of review cycles prior to approval, and shorten the overall time to approval.*" We cannot emphasize enough the importance of timely notification of deficiencies. Depending on the nature of the deficiencies, it may be possible for the applicant to respond with the necessary information in sufficient time to allow for approval within the first cycle. This may even be possible when there are significant deficiencies, but only if the applicant is given timely notification.

Line 115: We believe that the GRMPs should emphasize not only the importance of the "successful completion of the first-cycle review," but more precisely the "successful completion of the first-cycle review resulting in approval of applications that meet the standards for safety and efficacy."

Lines 127-128: We strongly disagree with the statement, "*It is important for applicants to understand that adhering to the GRMPs will not modify the first-cycle review outcomes for applications with substantive scientific or regulatory deficiencies.*" We believe that actual experience has demonstrated just the opposite...a well managed review process with prompt communication of deficiencies can lead to successful resolution of issues within the first cycle. This will usually depend on the nature of the deficiencies, timely notification of the applicant, and the applicant's ability to respond with complete, high quality information on a timely basis.

Lines 133-135: While we generally agree with the emphasis on applicants submitting a complete application upon initial submission, we recommend the FDA also acknowledge the innovative steps it has taken to provide for earlier review of specific reviewable units of an application through such mechanisms as the Fast Track process and the Continuous Marketing Application pilots. Additionally, we believe the term "expected information" requires clarification. If "expected information" is in reference to information requested in prior communication with the agency, we recommend it be stated as such.

Line 137: We recommend that FDA replace the words "essentially eliminate" with "reduce". The revised sentence would read, "Submission of a complete application should *reduce* the need for unsolicited or unexpected amendments..." Even with a complete, high quality application, it is difficult, if not impossible, to anticipate all requests by review personnel to clarify or provide additional data.

- Lines 145-157: We believe the language limiting submission of planned amendments to situations where FDA agrees there is a valid public health urgency to expedite availability of the product is much too restrictive. The draft guidance reads, "*Such requests...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.*" Planned amendments to submit updates of stability data or long-term safety data are fairly common and can usually be accommodated within a first-cycle review (provided they are not submitted too late in the review cycle). We therefore strongly recommend that the sentence quoted above be deleted. However, we do generally agree that submission of planned amendments should be minimized, and the timing of their submission should be discussed in advance so that the review division can determine the impact on review timelines and workload.

- Lines 153-158: We believe the statement that FDA retains authority to review amendments, solicited or unsolicited, during the first cycle is too restrictive. While this might technically be correct, we believe the emphasis should be just the opposite, i.e., to complete the review of all amendments during the first cycle whenever possible. In reality, the vast majority of amendments are *unplanned* amendments that are submitted in response to direct requests from FDA for information or additional data. In the spirit of making safe and effective drugs and biologics available to the patient expeditiously, we recommend every effort be made to review amendments within the first cycle. FDA has authority to extend the cycle by 90 days if a major amendment is submitted during last 3 months of the review cycle. We recommend that the sentence beginning on line 154 be revised to read, "*FDA will generally make every effort to complete the review of all amendments submitted during the first cycle, but may decide to defer review of amendments to a subsequent review cycle when there are extenuating circumstances, such as when there are significant deficiencies that otherwise preclude approval that are not addressed by the amendment.*"

- Additionally, we do not agree with the statement that FDA may decide to defer review of amendments based on competing workload priorities and resource limitations (line154-158). The significant increase in user fee revenues that the agency will receive under PDUFA III should fund adequate staff resources to handle the application review workload.

- Lines 160-161: We recommend removal of the phrase, "to delay initial submission beyond a corporate target date"; the reference to corporate target date does not serve a useful purpose and may be misconstrued. Alternatively, we suggest modifying this sentence as follows, "*In some cases, submitting a complete application may require a decision by the applicant to postpone the initial submission.*"

Section IV - Process Principles

(IV.A Presubmission)

- Lines 211-221: We agree that encouraging major milestone meetings such as end-of-phase 2 and pre-NDA/BLA is important, and recommend that FDA expand the guidance to also acknowledge the value of other opportunities for meetings during development (e.g., End of phase 1, and others as needed).

- Line 276: We believe the wording "...to inform the exchange of information"...needs clarification. We suggest revising this sentence to read, *"To facilitate good review management, it is recommended that the applicant present a clear, concise background package to allow for a productive exchange of information."*

- Lines 284-285: We recommend revising the sentence, "The applicant is strongly encouraged to describe both the strengths and weaknesses..." to read, "*The applicant is encouraged to provide a balanced summary that objectively describes the content of the proposed application.*" In reality, the applicant is often not able to anticipate what FDA may perceive to be a weakness in the data, but the applicant should be encouraged to identify any issues faced during the development process and explain how they were addressed.

- Lines 323-331: Regarding pre-submission communications, the draft guidance states that "FDA's recommendations are best followed in their entirety; partial adherence to FDA recommendations may significantly undermine the potential benefit of pre-submission communications". We believe this wording is overly restrictive, discouraging the applicant from exploring alternative approaches. We recommend replacing it with more flexible language advising that the applicant should inform FDA if it elects to pursue an alternative approach and explain the basis for the decision.

- Lines 354-356: In addition to the applicant receiving an acknowledgement letter containing the date of receipt and assigned NDA/BLA number, we suggest also sending a receipt for the user fee payment to the applicant. We recommend FDA describe the mechanism for informing the applicant that the user fee payment has been accepted and that the filing review is progressing.

(IV.B. Application Receipt Process)

- Lines 351-352 and 379-380: We believe the assignment of a regulatory project manager and review team "as soon as possible" is too vague. We recommend identifying a specific time frame, e.g., within 1 or 2 days for the RPM, within 3 days for the review team and communicating these time frames to the applicant.

- Lines 363-373: Please clarify who performs the "administrative review" function for CBER. If there is a similar process, we suggest also describing it. We also recommend outlining the components of the "administrative review" to aid sponsors in preparing a quality application and to promote consistency of review within the FDA.

- Lines 398-419 and 423-426: We believe details for identifying the need for and requesting consult reviews, and the timing for such reviews should be more specific.

Unless managed effectively, consult reviews can result in issues being raised very late in the first cycle review, leaving virtually no possibility of resolving them without undergoing another cycle. We recommend that the guidance provide a specific time frame for issuing requests for consult reviews (allowing exceptions for those instances where the need for a special consult can not be immediately recognized). In addition, we recommend that the guidance specify when recommendations from consult reviewers must be provided back to the primary review division. We believe this has to be planned to occur well in advance of the action date to allow sufficient time to communicate questions to the applicant, for the applicant to respond, and for the relevant reviewer(s) to evaluate the response prior to the first cycle action date. Consistent with the goal of improving transparency of the review process, we also recommend informing the applicant of any requests for consult reviews.

Lines 411-419: We acknowledge the agency's plans to develop procedures and guidance relative to the PDUFA III goals related to risk management. Nevertheless, we recommend that the GRMP guidance include discussion of how review of risk management plans should be integrated with planning the review process. We suggest the guidance provide recommendations for the timing of review and how feedback on risk management plans will be communicated to applicant, and note that an amendment to a risk management plan will not, by itself, trigger an extension of the review clock in accordance with PDUFA III performance goals. Additionally, we recommend that all advice on GRMP's flow through the review division to assure that all agreements are understood by all parties.

Lines 428-430: We recommend outlining a process in the guidance for how and when FDA will communicate to the applicant about inspections of clinical, nonclinical, or biopharmaceutics research sites.

Lines 430-431: We believe the wording indicating requests for inspections should be made early in the review cycle is too vague. If inspections are initiated too late in the first cycle, this is another activity that can unnecessarily lead to a second cycle. We recommend the timing for initiating requests for inspection, as well as time frame for receipt of inspectional results, be more specific.

Lines 442-444: We believe timing for deciding review priority ("as soon as possible") should be more specific. For priority reviews, in particular, it is important for the review team to be aware of the review timelines.

Lines 502-504: Due to the more compressed review schedule for priority applications, we suggest adding a recommendation for a faster target for filing meetings, e.g., within 30 days after receipt of the application if not sooner. Some review divisions have already done this, and it allows more time for the comprehensive scientific review between the filing meeting and the PDUFA action goal date.

(IV.C. Filing)

- Line 556: We recommend the Office Director always be consulted on a refuse-to-file decision. Accordingly, we suggest revising this sentence to read, "*All refuse-to-file decisions must include consultations with the office director.*" We believe consultations should be documented and provided to applicants.

- Lines 587-589: As noted for lines 502-504, we suggest clarifying "in some cases" (e.g. for priority review applications) the review team should schedule the filing meeting sooner (e.g. within 30 days).

- Lines 609-618: We endorse the principle of providing early notification of deficiencies prior to the filing meeting. Timely communication is essential for giving the applicant the opportunity to address correctable deficiencies in advance of the filing meeting.

- Lines 626-628: We recommend clarifying the wording to clearly indicate that all substantive issues/questions should be communicated to the applicant. The wording in the draft guidance could be interpreted to mean that only those issues pertaining to the filing decision should be communicated.

- Lines 634-640: We recommend revising this paragraph to clarify that a refuse-to-file letter should only be considered when there are major deficiencies that cannot possibly be remedied by the filing date, and that issues involving scientific interpretation are not ordinarily the basis for a refuse-to-file decision but should be addressed as part of the comprehensive review.

- Lines 649-654: The sentence starting with, "The applicant should be aware..." conveys unwarranted emphasis that amendments containing responses to filing review issues may not be reviewed during first cycle. We expect that as a result of receiving early notification of the deficiencies, the applicant would be able to respond sooner and the FDA would be in a better position to complete its review of the entire application (including amendments) during the first cycle. The point of including early communication as a PDUFA III goal was to ensure that there will be adequate time for applicants to respond early in the review cycle, and we recommend FDA make every effort to review such responses during the first cycle.

(IV.D. Review Planning)

Overall, we believe this section is vague and would benefit from providing details on the following points: Timing, Responsibility (who is responsible for the planning), Workload and Staffing (how are these factors assessed by the review teams?), GRMP project plan (is a written project management timeline prepared? By whom? Who monitors the progress?).

- Line 680: We agree that the review process should be organized early. In addition, we recommend that complex products, such as combinations that may require cross-center

coordination be assigned to a project manager(s) who has expertise on negotiating across centers, divisions and disciplines to achieve timely outcomes. These products often represent some of the most scientifically innovative breakthroughs, yet within the FDA process, they are only grouped within traditional center or drug divisions and rely upon cross consultations rather than relying upon a dedicated staff or set of experts.

- Lines 694-700: We recommend expanding the list of bulleted items to include a) consult reviews, b) requests for inspections, c) plans for labeling interactions with the applicant, and d) discussion of post-approval commitments (when applicable). We also suggest that an example timeline be included depicting when the most critical activities should occur in a model first cycle review. 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 with the review planning activity.

- Lines 718-719: BIO believes that the lines describing FDA managing the communication of concerns to the applicant is too vague. We believe it is important to stress as GRMP that early communication to the sponsor is critical if deficiencies in the application are identified (see also our comments on lines 839-844).

- Lines 719-721: It is not possible for FDA to manage the timing of applicant responses. We therefore recommend replacing "timing" with "review." While the applicant may not need to know of each internal FDA process, greater overall transparency during the initial filing and review would improve an applicant's understanding of the critical review activities and may help the applicant to prepare to have appropriate resources available to respond to any agency queries.

(IV.E. Review)

- Lines 747-748: We recommend clarifying how the communication between primary and secondary reviewers should occur, e.g., through regularly scheduled meetings, team meetings, ad hoc updates, all of these approaches?

- Lines 839-844: We recommend changing the subheading from "Use of Information Request and Discipline Review Letters" to "*Communication with Applicants during the Review.*" We suggest this section emphasize early communication of review issues and questions to the applicant rather than waiting until the end of the review cycle, and identify information request and discipline review letters as two of the available mechanisms for such communication. We believe this should not preclude the use of other less formal means of communication such as secure e-mail, fax, telephone contacts, etc. Including these other less formal options for communication is extremely important, as in some cases crucial time is lost while waiting for a formal letter to be processed.

- Lines 887-891: As noted elsewhere in these comments, we believe the draft guidance places undue emphasis on FDA's discretionary authority to decide whether to review amendments during first cycle. As stated earlier, BIO believes that it would be more appropriate to emphasize that FDA will make every effort to review amendments unless the timing of their submission or their magnitude precludes the possibility of completing their review during the first cycle. We believe that implementation of GRMPs will result in earlier communication of deficiencies and requests for information, which will result in a corresponding earlier receipt of the applicant's response. These factors should enhance FDA's ability to complete its review and approve safe and effective products within the first review cycle. As noted earlier, FDA has the authority to extend the clock by 90 days for special circumstances when major amendments are received during the last 3 months of the review cycle and additional time is needed to complete the review.

- Lines 904-907: The sentence stating, "*The review division retains the authority to review amendments that contain material that should have been included with the initial application submission....*" implies that the review division may simply choose not to review an amendment on the basis of a subjective determination that the amendment included material that should have been included in the original application. We believe that this language is inappropriate and unnecessary. As noted previously, it is rare that an applicant can anticipate every request for information, clarification, or for additional data that a reviewer may make during the review. Such requests are a normal aspect of the review process, and we believe it would be better to emphasize the need for prompt communication of such requests by the review division and timely responses by the applicant.

- Lines 958-959: We do not agree with the statement that conveyance of FDA interim review process timelines should be discouraged. Sharing this kind of information helps the applicant understand the process, is consistent with operating in a more transparent manner, and does not interfere with ongoing review activities. While the applicant does not necessarily need to know all the details of FDA's internal processes, sharing information on significant activities removes much of the mystery for the applicant and can even be helpful to the review division. For example, sharing information on the timing for an internal meeting to discuss the proposed labeling can help the applicant anticipate when comments may be received and thus ensure that the appropriate company experts are available to prepare a timely reply or participate in a teleconference. Accordingly, we recommend that this sentence be deleted.

(IV.F. Advisory Committee Meetings)

- Lines 966-968: We recommend changing the words "generally is" (line 967) to "should be". The revised sentence would read, "*The decision regarding whether to present an application to an AC should be made ...early in the first cycle review process.*" We further recommend adding a sentence to make it clear that the applicant should be promptly notified in order to allow timely planning and preparation of materials for the AC meeting.

- Lines 1015-1021: We believe the language about providing the review division's background package to the AC members and the applicant is too vague. We recommend deleting the word "generally" in line 1016. We also recommend providing more specific guidance on the timing for when the questions and division background package should be provided to the applicant and to the committee (lines 1019-1021).

- Lines 1035-1037: BIO agrees that sharing information and presentations in advance of the advisory committee meeting to avoid unnecessary overlap and redundancy is useful and recommends strengthening the wording, i.e., "*Consistent with this goal it is recommended that the review division and the applicant work together....*"

- Line 1052: Please add, "subsequently" ... "actions that *subsequently* occur on an application"

- Lines 1060-1066: When FDA's actions are at odds with the Advisory Committee's recommendations, the draft guidance states (line 1063), "The division should also send a brief memorandum to those members who participated in the meeting. The memorandum should outline the regulatory action taken and provide a brief description of the rationale for such action." We recommend that this be expanded to indicate that the applicant should also be provided a similar explanation of the review division's actions and the basis for deviating from the Advisory Committee's recommendations.

- Lines 1085-1086: We believe the sentence reading, "The review division generally will share its presentation with the applicant in advance of the AC meeting" is too vague. We recommend changing "generally will" to "*should also*".

(IV.G. Wrap-Up and Labeling)

- This section of the draft guidance does not contain any discussion of post-approval commitments. We believe this is a significant aspect of the late phase of the review process and recommend that it be covered by the GRMP guidance. Post-approval commitments often involve major commitments to conduct studies that may take several years to complete. They also may require a significant commitment of resources by the applicant. Failure to include in a well managed review process time for communication between the FDA and the applicant on potential post-approval commitments could result in hasty commitments leading to poorly conceived studies that are not feasible to complete, or that are not capable of providing the desired information.

  Accordingly, we recommend adding text to the guidance to clearly indicate that planning for discussion of potential post-approval commitments should be included in planning the review process. Sufficient time should be planned for internal discussion within FDA, interaction with the sponsor, consultation with the Office Director, and for negotiation of the final commitments with the applicant (similar to, and parallel with, the process for labeling negotiation). Specific guidance should be included on how far in advance of the PDUFA action goal date the suggested post-approval commitments should be communicated to the sponsor. We recommend that the review division's preliminary

ideas on the need for, and nature of, potential post-approval studies be communicated to the applicant 30 days in advance of the PDUFA action goal date to allow for meaningful evaluation of the purpose and feasibility of any proposed studies. Following the applicant's response, and after the Office Director's input (for NMEs) has been obtained, additional interactions with the applicant should occur 2 weeks prior to the action goal date to resolve any differences of opinion and reach agreement on the final commitments..

- Lines 1126-1133: We believe the wording regarding planning for labeling communications is too general and should be clarified by adding that times for labeling teleconferences should be pre-planned well in advance. We recommend specifically stating the timing for initiating the labeling negotiation process, e.g., at least 30 days in advance of action date.

- Line 1140: We recommend revising the sentence beginning with "It is recommended that..." to read, "*Review teams should schedule internal labeling meetings...*" We also recommend replacing the words "...well in advance of the final action goal date..." with more specific guidance. It would be helpful to FDA review teams to have specific guidance on when such interactions should commence.

- Lines 1155-1158: BIO agrees that applicants should be responsive to FDA requests to ensure timely completion of application reviews. However, requests for submission of extra items such as promotional materials, as mentioned in line 1057, can inappropriately preclude FDA from taking an action of approval. Only products approved under the accelerated approval regulations (subpart H) require submission of promotional material prior to approval.

- Lines 1166-1167: For effective planning and management of the process, we recommend adding that specific dates and times for labeling teleconferences should be pre-scheduled so that both the review division and applicant know when these interactions will occur and can plan accordingly.

  It would also be useful to expand the guidance on how the labeling negotiation should be conducted. We agree that it is important for both the FDA and the applicant to explain the basis for any recommended changes. For the initial exchange of review division comments and the applicant's response, it is generally most expeditious to convey the comments by facsimile or secure e-mail. If there are still unresolved issues, a teleconference or face-to-face meeting should be arranged in order to reach closure on the remaining items. For the final negotiation, it is important for both the FDA and the applicant to have representatives participating who are authorized to make decisions and reach agreement on the final wording.

(I.V.H. Action)

- Lines 1258-1267: We agree with the emphasis in this paragraph on completion of review team and consult reviews, and inspections within the planned timelines. As noted in our

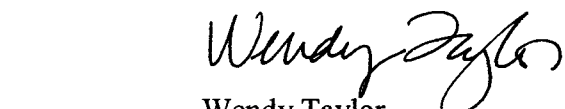
comments on lines 694-700, we recommend that some of these points from a planning perspective also be covered in section IV.D. on *Review Planning*, especially regarding the consult reviews and inspections.

- Lines 1276-1281: We acknowledge and support FDA's plans to develop guidance on post-marketing study commitments. Nonetheless, as noted in our comments above pertaining to section IV.G. *Wrap-Up and Labeling*, we recommend including guidance in the GRMP document in advance of availability of the planned detailed guidance. Specifically, this is a critical activity that deserves ample time for careful thought and discussion between the FDA and the applicant. We recommend, at a minimum, inserting recommendations to address the timing of such interactions (e.g., providing preliminary feedback to the applicant 30 days in advance of the PDUFA action goal date, consultation with the Office Director, and further communication with the applicant at least 2 weeks prior to the action goal date to negotiate and reach final agreement on the proposed studies).

- Line 1379: For the sake of clarity, we recommend deleting the words "wish to." The revised sentence would read, "*Following receipt of an action letter, the applicant may hold a brief teleconference with...*" We suggest the guidance be more specific about the mechanism for requesting and granting this teleconference. We believe that, in this instance, following standard meeting management goals and/or submission of a background document is not warranted.

In closing, BIO appreciates this opportunity to comment on the draft guidance on *Good Review Management Principles for PDUFA Products*. We commend the agency for the progress made in developing the draft and remain enthusiastic about the potential this initiative has to improve the efficiency of the regulatory review process in the future. BIO agrees with the spirit of the GRMP initiative, and we believe that it will, when implemented, be in the best interest of patients who would benefit from faster availability of safe and effective new therapies. We look forward to seeing the final guidance, and would be glad to work with the agency to provide further input or clarification of our comments, as needed.

Sincerely,



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