



**1225 Eye Street NW, Ste. 400
Washington, DC 20005**

October 18th, 2004

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

Re: Docket No. 2004N-0267, Federal Register: July 20, 2004 (Volume 69, Page 43351)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). 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 healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) Proposed Rule on Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications.

We have a number of comments detailed below, referenced to the regulatory provision proposed to be amended.

§314.60 – Amendments to an unapproved application, supplement, or resubmission

FDA states in this proposal that submission of a major amendment within 3 months of the end of the initial review cycle constitutes an agreement by the applicant to extend the review by 3 months. BIO agrees that this is an accurate interpretation of current Prescription Drug User Fee Act (PDUFA) goals, which state that submission of a major amendment constitutes an agreement to extend the date by which the agency is required to make a decision “for the amount of time necessary to review the new information,” not to exceed 90 days. However, we also note that these and other goals and attendant time frames could be changed with the development of future PDUFA goals. In fact, time frames agreed on in PDUFA negotiations historically have taken precedence over whatever time frames existed prior to that, a reality acknowledged by FDA in its proposed revision to §314.100(a)(2) (time frames for reviewing applications and abbreviated applications). Given this historical precedent, as well as the current regulations which provide for extensions of review times upon submission of a major amendment (but do not identify an exact time frame) and that specific time frames are negotiated under PDUFA and included in PDUFA goals, we recommend against fixing any specific time frame, including the current 3 month PDUFA time frames, in regulation. If the agency believes it is necessary to codify PDUFA goals with respect to extensions, we recommend simply adding a statement to current regulations such as, *“For applications that are human drug applications, as defined in section 735(1)(A) and (B) of the act, or supplements to such applications, as defined in section 735(2) of the act, any extension of review as a result of submission of a major amendment shall be consistent with the agency’s user fee performance goals for reviewing such amendments.”* This approach mirrors the agency’s proposed revision to the regulation governing timeframes for review (§314.100) and allows the regulations to remain flexible in light of changing PDUFA goals.

In addition, FDA proposes to enhance its authority, under proposed §314.60, by asserting that it can unilaterally defer to a subsequent review cycle the review of major amendments received within 3 months of the end of the initial review cycle [(§314.60(b)(1)], the review of a major amendment submitted more than 3 months before the end of the initial review cycle [(§314.60(b)(2)], minor amendments regardless of the timing of their submission [(§314.60(b)(3)], and any amendments to supplements other than efficacy supplements [(§314.60(b)(4)].

Nowhere in the current PDUFA performance goals or in any legislative history associated with PDUFA is there indication that Congress intended FDA to have the unfettered authority to defer review of an amendment to a subsequent cycle or even that such an optional authority, with no additional discussion or oversight, was ever contemplated during PDUFA negotiations. On the contrary, the very use of the word “extension”, as opposed to the words *extension or deferral*, implies that the specific provision in the PDUFA goals for *extension* of review time when a major amendment is received within the last 3 months of the review cycle was intended to encourage a single, contiguous review leading to a complete response. A goal of accommodating other amendments,

such as those received earlier in the review cycle or minor amendments, is implied by the absence of reference to extensions of review time in such situations.

While emphasizing that unlimited FDA authority to defer review is inappropriate, we do recognize that there may be a few situations where deferral because of certain amendments may result in more efficient review and more effective use of both agency and industry resources. If FDA believes that there are *specific conditions* under which a deferral will result in a more efficient and effective review, BIO suggests that any such conditions be clearly defined in the regulation.

We believe the following situations may represent conditions under which deferral of review may be considered:

[§314.60(b)(1)] - a major amendment to an application or supplement, received within the last 3 months of the initial review cycle, (a) that amends the technical section or sections of the application in which FDA review has identified deficiencies that are of sufficient magnitude to cause the application not to merit approval during the current review cycle, and that, on its face, does not contain the information necessary to put the application in condition for approval or (b) that amends a technical section of the application other than the technical section or sections in which FDA review has identified deficiencies that form the basis for not approving the application, but where review of the amendment will not result in approval during the current review cycle or for which, under prevailing PDUFA goals, FDA cannot extend the review cycle (for example, a second major amendment within the last 3 months under current PDUFA goals).

[§314.60(b)(2)] – a major amendment received more than 3 months before the end of the initial review cycle but when FDA’s review of the application or supplement is sufficiently complete to have identified one or more major deficiencies, such as a failed pivotal trial, that are not addressed by the major amendment and that are unlikely to be addressed during the current review cycle because of the need for significant additional research or development.

[§314.60(b)(3)] – a minor amendment received within 1 month of the end of the review cycle or that, on its face, does not contain information adequate to put the application in condition for approval during the current review cycle because of the nature of deficiencies already identified by one or more discipline reviews.

[§314.60(b)(4)] - an amendment to a supplement other than an efficacy supplement that is received within 1 month of the end of the review cycle or that, on its face, does not contain information adequate to put the application in condition for approval during the current review cycle because of the nature of identified deficiencies.

Regardless of whether any specific examples such as those described above are adopted in the final rule, we strongly believe that the referenced sections should emphasize that FDA will ordinarily strive to complete a full review of the application, including any

submitted amendments, by the PDUFA goal date. Deferral of review of an amendment should only be invoked when the amendment is submitted so late in the cycle that it can not possibly be reviewed by the PDUFA goal date, or if it can not possibly contribute to an approval decision because of the existence of major deficiencies that could not possibly be addressed within the same review cycle.

Finally, BIO believes the Final Rule should require written notification to the applicant when FDA determines that deferral of review is appropriate and necessary. A decision to defer review of an amendment to a subsequent cycle constitutes an action decision since it represents FDA's conclusion that the application or supplement will not be approved in the current review cycle. The decision also implies that the review of the application is sufficiently complete at the time of the deferral to identify critical deficiencies that are not addressed by the amendment and that FDA believes cannot be addressed by further amendments during the current review cycle. Therefore, we believe a written notification of deferral of review of an amendment also should describe the deficiencies that preclude approval.

314.110(b)(1)(iii) - Resubmission of a Supplement other than an Efficacy Supplement

Proposed 314.110(b)(1)(iii) states that resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the applicant to start a new 6-month review cycle. We do not believe this is appropriate for certain applications in view of the existing PDUFA goals. For example, under the current goals FDA is to act on 90 percent of original manufacturing supplements that require prior approval within 4 months of receipt. When a complete response letter is issued resulting in a subsequent resubmission, the proposal would establish a review clock for the resubmission that exceeds the time frame that was applicable for review of the original supplement by 2 full months. The need for a lengthier period of time for review of the resubmission is unjustifiable, especially considering that many of these resubmissions contain a relatively small amount of data that is necessary to answer specific questions resulting from the initial review cycle.

BIO therefore recommends that proposed 314.110(b)(1)(iii) be re-worded to state that the length of the review cycle for the resubmission will not exceed that which was applicable for the original application. We further recommend that FDA implement a type 1/type 2 classification scheme for prior-approval chemistry/manufacturing supplements. This would be similar to the approach used for resubmissions for original applications and efficacy supplements, except the review cycle should be 2 months for a type 1 resubmission and 4 months for a type 2 resubmission.

§314.110(c), §601.3(c) - Failure to take action

BIO opposes the proposed provisions (sections §314.110(c) and §601.3(c)) under which FDA will consider failure of an applicant to respond within a specified time (1 year) tantamount to a request by the applicant that the application be withdrawn. Our reasons for opposing this are outlined below.

First, the absence of resubmission within 1 year of receipt of a Complete Response letter cannot reasonably be characterized as failure to take action. Depending on the deficiencies described in the Complete Response letter, a sponsor may invest several months reaching agreement with the Agency on additional work that would best address the deficiencies. When an applicant needs to plan, design, conduct, analyze, and report an additional study or to develop and validate additional testing procedures (sometimes with input from the agency), it may well be more than a year before the application can be resubmitted. The proposal does not appear to address these possibilities at all.

Second, the purpose of this provision is unclear. No justification or rationale is included in the preamble to the proposed rule.

Third, the proposal appears to favor speed over quality of response by the applicant. However, because withdrawal of an application has a variety of serious negative connotations for an applicant, this approach almost certainly will have the (unintended) effect of reducing the quality of resubmissions as a result of a push to meet the 1-year deadline.

Fourth, because deeming an application withdrawn under this provision is optional, differences among Centers, Divisions within Centers, or individual review teams may create an uneven playing field in which some applications are withdrawn while other equally situated applications are not. No clarifying information is provided to guide FDA's interpretation of this proposal.

The decision to withdraw an application rests with the applicant and should not be one unilaterally made by FDA. If FDA believes the current situation regarding delayed responses from applicant merits action, BIO suggests the following possible alternatives. (1) Add to Parts 314 and 600 the option for the applicant to notify FDA, within a specified time frame, of its intent to amend the application. In a case where the application is not resubmitted within 1 year, FDA may require the applicant to provide annual confirmation of its intent to resubmit, including an estimate of the time frame for resubmission. Applicants would then be on notice officially that absent such affirmative notification(s) from them, FDA may consider their applications withdrawn if they are not resubmitted within 1 year. (2) Under "*failure to take action*," require FDA to send prior notification to the sponsor requesting a reply within a specified time frame. This would allow the sponsor to verify its intention to resubmit (along with its estimated time frame for resubmission) or to agree to withdrawal. The notification should specify that failure of the sponsor to reply within a stipulated time would constitute the sponsor's request for withdrawal.

314.3 – Definitions

Class 1 Resubmission: The definition includes a list of items that qualify a resubmission as “Class 1.” Because the items are separated by commas and the list is concluded with the conjunction “and,” it can be interpreted as meaning that a Class 1 Resubmission is one that contains ALL the items in the list. BIO recommends revising the definition as follows:

Class 1 resubmission means the resubmission of an application, following receipt of a complete response letter, that contains **one or more of the following items**: final printed labeling, draft labeling, ...

Complete Response Letter: The agency proposes to define this as: “A *written communication to an applicant from FDA usually identifying all of the deficiencies in an application or abbreviated application that must be satisfactorily addressed before it can be approved.*”

Inserting the word “usually” into this definition is contrary to the plain meaning of “complete response.” Any response that doesn’t identify all the deficiencies identified in an application isn’t a complete response by any common understanding of the meaning of “complete.” Use of this sort of vague language makes the regulation impossible to interpret and leaves it open to inconsistent application across FDA review divisions.

Current user fee goals do not include similarly vague language but instead reflect FDA’s commitment to “review and act on” certain percentages of applications within specified time frames. The term “review and act on” is defined in both the PDUFA III and MDUFMA goals letters as being “understood to mean the issuance of a complete action letter after the complete review of a filed complete application.” The letters further state that a Complete Response letter will summarize all of the deficiencies remaining and “where appropriate, describe actions necessary to place the application/supplement in a condition for approval.”

BIO recognizes that there may be specific, limited circumstances when it is reasonable for FDA to have the authority to postpone certain aspects of a “complete review.” For drug products, these conditions are described under proposed §314.110¹ and are limited to conducting inspections and reviewing labeling. Similarly, for biological products,

¹ Under proposed 314.110 – “Complete response letter to the applicant”, subsection (a) states, “FDA will send the applicant a complete response letter if the agency determines that we will not approve the application or abbreviated application in its present form for one or more of the reasons given in §314.125 or 314.127 respectively.” Subsection (a)(1) – “Description of specific deficiencies” states: “A complete response letter will describe all of the specific deficiencies in an application or abbreviated application, except as stated in paragraph (a)(3) of this section.” Subsection (a)(3) – “Inadequate data” says, “If FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling.”

CBER SOPP “Regulatory—License Applications Complete Review and Issuance of Action Letters,” SOPP 8405 (Version #4, September 20, 2004),² limits such conditions to testing of submitted product lots, pre-licensing inspections, and evaluation of final printed labeling.

BIO strongly urges that the definitions of Complete Response Letter for drug and biologic products specifically note those aspects of a complete review that may be postponed while allowing the agency to issue the action letter and not employ vague and uninterpretable language.

§314.100 – Timeframes for reviewing applications and abbreviated applications

We recommend further clarification be included in the rule to address situations in which an applicant chooses to withdraw an application after receipt of a complete response letter under §314.110(b)(2). Resubmission is defined in §314.3 as resubmission of an application following receipt of a complete response letter. Presumably, if the complete response letter is followed by withdrawal of the application, the subsequent submission of “the same” application would also constitute a “resubmission.” For clarity, FDA should consider adding, “*Except when preceded by a complete response letter, applications withdrawn prior to approval that are submitted again for the same product are not considered resubmissions as defined in §314.3(b) of this part.*” A similar provision should be included in Part 600.

§314.110 – Complete response letter to the applicant

It is unclear whether the complete review includes review of information submitted in major amendments submitted prior to the final 3 months of the review cycle or minor amendments (which do not trigger extensions under either the current PDUFA goals or the proposed rule). In view of the fact that, under current user fee goals, certain amendments do not result in extensions of the review cycle, we believe it is inadvisable to define the scope of material included in a complete response letter in terms of “amendments for which the review cycle was extended.”

² SOPP 8405 states, “Action letters are the result of complete Agency review of applications or supplements and stop the review clock. **Complete Response Letter** - This letter will be issued when the complete review indicates that there are deficiencies remaining that preclude the approval of the application or supplement at that time. The Complete Response Letter will: Summarize all of the deficiencies remaining, and where appropriate, describe actions necessary to place the application/supplement in a condition for approval. **Approval Letter** - Following completion of all aspects of the review process, including testing of submitted product lots, pre-licensing inspection and evaluation of final printed labeling or a suitable alternative, an approval letter will constitute the final action.

FDA request for comment on disclosure

Currently, FDA does not disclose the existence of an application or abbreviated application until it has issued an approvable letter unless the existence of the application or abbreviated application previously has been publicly disclosed or acknowledged by the applicant or sponsor. Under the proposed rule, FDA would disclose the existence of an application after issuance of a tentative approval letter or an approval letter. FDA would not disclose the existence of an application following issuance of a complete response letter unless the existence of the application has been previously disclosed or acknowledged by the applicant. BIO agrees with this proposal.

In conclusion, we appreciate the opportunity to provide our comments on this proposal and look forward to continuing to work with the agency as it proceeds toward publication of a final rule. If we may be of any further assistance, please do not hesitate to contact us.

Sincerely,

A handwritten signature in cursive script that reads "Sara Radcliffe".

Sara Radcliffe
Managing Director
Science and Regulatory Affairs