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

Re: Docket # 2004N-0267; Proposed Rule; Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications: 69 Federal Register 43351; July 20, 2004

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing over \$32 billion in 2003 to discover and develop new medicines, our member companies are leading the way in the search for cures.

PhRMA is pleased to offer the following comments on the above noted proposed rule. The need for this regulatory change is a result of agreements reached between the Food and Drug Administration (FDA) and the pharmaceutical industry during the discussions that resulted in the reauthorization of the Prescription Drug User Fee Act (PDUFA) in 1997. The reauthorization was part of a broader piece of legislation, the Food and Drug Administration Modernization Act. In an accompanying letter to Congress, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) agreed to change their regulations to provide for the issuance of either an approval or a "complete response" action letter at the completion of the review cycle for an application.

Comment 1: -- §314.60 – Amendments to an unapproved application, supplement, or resubmission

1. Revised §314.60(b)(1) would state:

"Submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement within 3 months of the end of the initial review cycle constitutes an agreement by the applicant under section 505(c) of the act to extend the initial review cycle by 3 months"

Comment: We agree 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 *under current Prescription Drug User Fee Act (PDUFA) goals*. Future PDUFA goals

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may retain or revise these specific time frames. Time frames agreed upon in PDUFA negotiations have historically taken precedence over existing regulatory time frames, a fact recognized in the proposed revision to §314.100(a)(2) [Timeframes for reviewing applications and abbreviated applications]. Under current regulations, 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 180 days.

Recommendation: Given that current regulations provide for extension of review times upon submission of a major amendment, and specific time frames are negotiated under PDUFA and included in PDUFA goals, we recommend against codifying the current 3 month PDUFA time frames in regulations. 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 regulation to remain in step with changing PDUFA goals.

2. Under proposed §314.60, the agency confers upon itself the authority to unilaterally defer to a subsequent review cycle,
 - a. the review of major amendments received within 3 months of the end of the initial review cycle [(§314.60(b)(1)),
 - b. the review of a major amendment submitted more than 3 months before the end of the initial review cycle [(§314.60(b)(2)),
 - c. minor amendments regardless of the timing of their submission [(§314.60(b)(3)), and
 - d. any amendments to supplements other than efficacy supplements [(§314.60(b)(4)].

Comment: There is no implication in the current PDUFA performance goals that Congress intended to confer upon FDA the unlimited option to unilaterally defer review of any amendment to a subsequent cycle or that there was industry agreement with deferral of amendment review. On the contrary, it is reasonable to conclude that the specific provision in the PDUFA goals for *extension* (not deferral) only 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. Providing no extension for major amendments received earlier in the review cycle or for minor amendments and the absence of provisions for deferral of review appears to represent agreement between FDA, Congress, and industry that FDA’s review goal was to accommodate the review of amendments within the time frame of the original goal date.

Recommendation: While PhRMA considers *unlimited, unilateral* FDA authority to defer review of amendments to be inappropriate, we recognize that there are conditions under which deferral of review of certain amendments may result in more efficient review as well as a more effective use of both agency and industry resources. We recommend, therefore, that

specific conditions under which FDA may defer review of amendments must be stipulated in the regulation.

PhRMA believes the following situations represent conditions under which deferral of review may be considered:

1. *[§314.60(b)(1)] - FDA may defer review of 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, where review of the amendment will not result in approval during the current review cycle; or*
 - c. *for which, under prevailing PDUFA goals, it cannot extend the review cycle (for example, a second major amendment within the last 3 months under current PDUFA goals)..*

2. *[§314.60(b)(2)] – FDA may defer to a subsequent review cycle the review of a major amendment received more than 3 months before the end of the initial review cycle when its 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.*

3. *[§314.60(b)(3)] – FDA may defer to a subsequent review cycle the review of a minor amendment that -*
 - a. *is received within 1 month of the end of the review cycle; or*
 - b. *on its face, contains information that is inadequate 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.*

4. *[314.60(b)(4)]—FDA may defer to a subsequent review cycle the review of an amendment to a supplement other than an efficacy supplement that –*
 - a. *is received within 1 month of the end of the review cycle; or*
 - b. *on its face, contains information that is inadequate to put the application in condition for approval during the current review cycle because of the nature of identified deficiencies.*

In addition, the final rule should require written notification of the applicant by FDA when FDA defers review of an amendment to a subsequent review cycle. A decision to defer review of an amendment to a subsequent cycle constitutes, in essence, an action decision. It represents FDA's conclusion that the application or supplement will not be approved in the current review cycle. It implies that the review of the application is sufficiently complete at the time of the deferral to identify critical deficiencies in the application that are not addressed by

the amendment and that FDA believes cannot be addressed by further amendments during the current review cycle. Therefore, we recommend that the written notification of deferral of review of an amendment should describe the deficiencies that have been identified in the application that preclude approval.

Comment 2, "Failure to take action"

1. Drugs –

§314.110(c) "*Failure to take action*" -- §314.110(b) describes "Applicant actions" available following receipt of a Complete Response letter. These include resubmission [314.110(b)(1)], withdrawal [314.110(b)(2)], or request an opportunity for a hearing [314.110(b)(3)]. If an applicant fails to take any such action within 1 year after receiving a complete response letter, FDA may, under proposed §314.110(c), consider such failure to be a request by the applicant to withdraw the application.

Under existing §314.110(a), applicants must respond within 10 days of receipt of an "approvable" letter, either by amending the application, notifying FDA of an intent to amend, withdrawing the application, requesting an opportunity for a hearing, or advising the agency that they agree to a specified extension while determining which response to make. FDA considers failure to respond within 10 days a request for withdrawal of the application.

The revised rule would rescind the opportunity for a sponsor of new drug application or supplement to inform FDA of its intention to respond to an FDA action describing deficiencies that need to be corrected to put the application in condition for approval.

2. Biologics –

Pursuant to section 601.3(c), FDA proposes

(c) Failure to take action. FDA may consider a biologics license applicant or supplement applicant's failure to either resubmit or withdraw the application or supplement within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application or supplement.

Comment: PhRMA opposes the proposed provisions under sections §314.110(c) and §601.3(c) for a number of reasons.

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.

Second, the proposed rule may favor “quickness” over “quality.” Because withdrawal of an application has negative connotations, this provision may have the unintended effect of reducing the quality of resubmissions as a result of a push to beat the 1 year deadline.

Third, because deeming an application withdrawn under this provision is optional, differences between Centers, Divisions within Centers, or individual review teams within Divisions 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 proposed rule.

Recommendation: The decision to withdraw an application rests with the applicant. We recommend modifying the proposed rule to replace the provision under which FDA may unilaterally consider an application withdrawn with one of the following provisions:

- a. under “*applicant actions*,” add the option to Part 314 and Part 600 for the applicant to notify FDA, within a prescribed time frame, of its intent to amend the application. In addition, if the application is not resubmitted within a year, require the applicant to provide annual confirmation of its intent to resubmit the application, including an estimate of the time frame for resubmission. Absent such notification, FDA may consider the application withdrawn if it is not resubmitted within 1 year; or
- b. Under “*failure to take action*” require FDA to send prior notification to the sponsor requesting a reply within a specified time frame to allow the sponsor to verify its intention to resubmit (along with its estimated time frame for resubmission) or to agree to withdrawal. Failure of the sponsor to reply to this notice within a stipulated time would constitute the sponsor’s request for withdrawal.

Comment 3: 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 has been previously publicly disclosed or acknowledged. 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 had been previously disclosed or acknowledged by the applicant.

Recommendation: We agree with the agency’s proposal not to publicly disclose the existence of an application until a tentative approval or an approval letter has been issued unless the existence of the application has been previously disclosed or acknowledged.

Comment 4: 314.3 – Definitions

1. *Class 1 Resubmission:* The definition includes a list of items that qualify a resubmission as “Class 1.” The items are separated by commas and the list is concluded with the conjunction “*and*.” This implies that a Class 1 Resubmission is one that contains ALL the items in the list. It would be better to revise 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, certain safety updates, stability updates to support provisional or final dating periods, commitments to perform Phase 4 studies (including proposals for such studies), assay validation data, final release testing on the last lots used to support approval, minor reanalyses of previously submitted data, **or** other comparatively minor information.*

2. *Complete Response Letter.* The agency would 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.”

Comment: 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 vague language is inappropriate because it makes the regulation impossible for the public to interpret and leaves the regulatory process open to inconsistencies in its application across divisions.

The user fee goals currently in effect for drugs and biologics, including licensed medical devices, do not include similarly vague language. Under the goals, FDA made a commitment to Congress, industry, and the public to “review and act on” a certain percentage of applications of various categories within specified time frames. For the purposes of the goals, the term “review and act on” is defined in both the PDUFA III goals letter and in the Medical Device User Fee Modernization Act (MDUFMA) Goals Letter as being “understood to mean the issuance of a complete action letter after the complete review of a filed complete application.” These goals further state that 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.”

PhRMA recognizes, however, that there are specific, limited circumstances under which it is reasonable for regulations to confer upon FDA the authority to postpone certain aspects of a “complete review.” For drug products, these conditions are appropriately described under proposed §314.110¹ and are limited therein to conducting inspections and review of labeling. Similarly, for biological products, CBER SOPP “Regulatory—License Applications Complete Review and Issuance of Action Letters,” SOPP 8405 (Version #4,

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.”

September 20, 2004),² limits such conditions to testing of submitted product lots, pre-licensing inspections, and evaluation of final printed labeling.

Recommendation: For the above reasons we recommend that the definitions of Complete Response Letter for drug and biologic products specify those aspects of a complete review that may be postponed while allowing the agency to issue the action letter. The recommended definitions are as follows:

Recommended definition – Drugs

Complete Response Letter means a written communication to an applicant from FDA identifying all of the specific deficiencies in an application or abbreviated application or supplement that must be satisfactorily addressed before it can be approved. A Complete Response letter may be issued without first conducting required inspections and/or reviewing proposed product labeling when FDA determines that the data submitted are inadequate to support approval as described in §314.110(a)(3) of this Part. Where appropriate, a complete response letter will describe the actions necessary to place the application in condition for approval.

Recommended definition – Biologics

Complete Response Letter means a written communication to the applicant from FDA identifying all of the specific deficiencies in a biologics license application or supplement that must be satisfactorily addressed before it can be approved. A Complete Response Letter may be issued without conducting testing of submitted product lots, required inspections, or evaluation of final printed labeling or suitable alternative.

Comment 5: §314.100 – Timeframes for reviewing applications and abbreviated applications

Revised § 314.100(a)(1) states, “Except as provided in paragraph (a)(2) of this section, within 180 days of receipt of an application under section 505(b) of the act or an abbreviated application for a new drug under section 505(b) of the act or an abbreviated application for a new drug under section 505(j) of the act, FDA will review it and send the applicant either an approval letter under § 314.105 or a complete response letter under § 314.110. This 180-day period is called the “initial review cycle.”

FDA goes on to state in revised § 314.100(a)(2), “...the initial review cycle will be adjusted to be consistent with the agency’s user fee performance goals for reviewing such applications and supplements.”

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.

Comment: PhRMA strongly objects to this proposed language extending the initial review cycle for drugs subject to user fees. Although the user fee performance goals recognize that FDA does not typically meet the statutorily mandated 180-day review timeframe, PhRMA does not believe it is appropriate to memorialize this in a regulation. Rather, the regulation should reflect the time period set forth in Section 505(c)(1) of the Federal Food, Drug, and Cosmetic Act, which clearly states that FDA shall make a decision “[w]ithin one hundred and eighty days after the filing of an application under subsection (b). . .” 21 U.S.C. §355(c)(1). Even if this statutory review period is regarded mainly as aspirational, PhRMA believes it is important to maintain it within the current regulations.

Revised §314.100(b) states, “*At any time before approval, an applicant may withdraw an application under §314.65 and later submit it again for consideration.*”

Comment: Further clarification should 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.”

In addition, we note that a similar provision is not included in Part 600 for biological applications.

Recommendation: 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 or the rationale for excluding it should be discussed in the preamble to the final rule.

Comment 6, §314.110 – Complete response letter to the applicant

§314.110(a)(2) “*Complete Review of Data*” – This subsection states:

“A complete response letter reflects FDA’s complete review of the data submitted in an original application or abbreviated application (or, where appropriate, a resubmission) and any amendments for which the review cycle was extended. The complete response letter will identify any amendments for which the review cycle was not extended that FDA has not yet reviewed.”

Comment: Under this description 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).

Recommendation: 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."

Comment 7: Absence of Definition of "resubmission" in 21 CFR §600.3

Proposed §601.3(b) states,

(b) Applicant actions. After receiving a complete response letter, the biologics license applicant or supplement applicant must take either of the following actions:

(1) Resubmission. Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter.

Comment: Describing resubmission of the application or supplement without any qualifying language appears to require resubmission of the original application or supplement, as opposed to resubmission of the response to the deficiencies identified in the complete response letter. Based on current practice and qualifying language proposed under section 314.110, it appears the intent of this provision is not to require resubmission of the original application or supplement.

Recommendation: PhRMA recommends clarification of this provision by adopting the same qualifying language proposed under section 314.110 describing resubmissions pertaining to drug applications. Specifically, we recommend inclusion of the following statement "[f]or purposes of this section, a resubmission means submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter." As recommended, section 601.3(b)(1) would read

(1) Resubmission. Resubmit the application or supplement, addressing all deficiencies identified in the complete response letter. For purposes of this section, a resubmission means submission by the applicant of all materials needed to fully address all deficiencies identified in the complete response letter.

PhRMA trusts that these comments are useful to FDA as the Agency moves forward to finalize this regulation.

Sincerely,

