

October 18, 2004

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



**RE: Docket No. 04N-0267  
Proposed Rule - Applications for Approval to Market a New Drug;  
Complete Response Letter; Amendments to Unapproved Applications**

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$3 billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays. With that intent, we offer comments on the following aspects of the proposed rule.

**Timing to Disclose the Existence of NDA/ANDA**

The Agency specifically invites comments on whether it would be appropriate to disclose the existence of an NDA/ANDA following issuance of a complete response (CR) letter and if so, what conditions, if any, should be placed on such disclosure.

*Comment: It is inappropriate for the Agency to routinely disclose the existence of an NDA/ANDA following issuance of a CR letter, before the application has been deemed to meet the scientific and technical requirements for approval under 505(b)&(j) of the Act. It is reasonable for the Agency to continue its current practice of routinely disclosing the existence of an NDA/ANDA following the issuance of an approval/tentative approval letter, not following issuance of a CR letter. This practice is consistent with the sponsor's and Agency's presumptions that before approval, the existence of an application is confidential commercial information. However, the Agency may disclose the existence of an NDA/ANDA following issuance of a CR letter, provided that the applicant requests that the Agency*

*disclose the application. Applicants must make this request within 10 days following receipt of a CR letter. This approach places the onus on the applicant to request the disclosure and should prevent inadvertent disclosure by the Agency prior to approval since disclosure at the CR stage will be the exception, not the rule.*

### **Agency Discretion to Defer the Review of Amendments to Unapproved Applications**

The proposal states that the submission of a major amendment to an unapproved NDA or efficacy supplement within 3 months of the end of the initial review cycle constitutes an agreement to extend the review cycle by 3 months. The proposal also provides that FDA may instead defer review of such an amendment until the subsequent review cycle. The same deferral option is proposed for major amendments submitted more than 3 months before the end of the review cycle, minor amendments, and amendments other than those for efficacy that are submitted more than 3 months prior to the end of the review cycle. *Subsequent review cycle* is defined as *from the resubmission of the application, efficacy supplement, or resubmission, following receipt of a CR letter to the issuance of either a second CR letter or an approval letter*. The Agency justifies these changes as codifying current policy on extending the review period when information is submitted before FDA issuance of an action letter.

*Comment: The proposed deferral options under 21 CFR 314.60 grant the Agency wide latitude to defer reviews of any type of amendment (major vs. minor) regardless of the timing of the submission as it relates to the end of the review cycle (within 3 months of goal date vs. more than 3 months prior to goal date) or the type of amendment (efficacy vs. other). The changes as proposed should not be codified. We consider unilateral deferrals to be inappropriate and request that the Agency explain the conditions under which reviews will be deferred, such as:*

#### **314.60(b)(1) For MAJOR amendments submitted within 3 months of the end of the review cycle:**

- *The FDA may not be required to review a major amendment that pertains to one section of the application if FDA has previously identified deficiencies in another section of the application that prevent first cycle approval.*
- *The FDA may not be required to review a second major amendment submitted within 3 months of the goal date with no accompanying extension of the review clock.*

#### **314.60(b)(2) For MAJOR amendments submitted more than 3 months in advance of the end of the review cycle:**

*As user fee performance goals only speak to the submission of a major amendment within 3 months of the end of the review cycle, the implication is that the review of major amendments submitted earlier in the review cycle can be accommodated in the original review timeframe. Therefore, the Agency should not defer the review of major amendments submitted well in advance of the goal date; this option should be deleted from the rule. However, if reasons for deferral exist, they should be explained in the regulations.*

314.60(b)(3) For MINOR amendments (submitted at any time in the review cycle):

*The FDA may consider deferring the review of minor amendments that are received late in the review cycle (e.g. within weeks of the goal date) when their review is not expected to impact the outcome of the review.*

314.60(b)(4) For amendments to supplements other than efficacy supplements:

*The FDA may consider deferring the review of amendments to supplements other than efficacy supplements that are received late in the review cycle (e.g. within weeks of the goal date) when their review is not expected to impact the outcome of the review.*

**Responses to Complete Response Letters**

In proposed 314.110(b), NDA and ANDA applicants may take one of three actions following receipt of a CR letter: (1) resubmit the application addressing all deficiencies, (2) withdraw the application, or (3) request an opportunity for a hearing. Failure to take one of the three actions within 1 year for NDAs (or 6 months for ANDAs) after receiving a CR letter is considered a request by the applicant to withdraw the application. Similar provisions are proposed for biologics in 601.3(b); a biologics applicant must take one of two actions: (1) resubmit the application addressing all deficiencies, or (2) withdraw the application. Failure to take one of the two actions within 1 year for BLAs after receiving a CR letter is considered to be a request by the application to withdraw the application.

Comment:

- *The proposal as written requires that sponsors be prepared to resubmit the application within 1 year as it does not contain an option through which to extend the time period. It does not contain a provision through which a sponsor may communicate an intention to amend the application per current 314.110(a). This is particularly important if the sponsor may need more than one year to address all deficiencies to resubmit the application.*

*We recommend that the Agency expand option 1 in 314.110(b) and 601.3(b) to permit sponsors to resubmit the application addressing all deficiencies or state their intention to do so, (if in the sponsor's best estimate, it will take more than 1 year to address all deficiencies). Although this provision may not be used often, it recognizes that sponsors may be working with due diligence beyond one year to address deficiencies identified in a CR letter.*

- *The proposal as written states that an application may be considered withdrawn by the Agency after 1 year has lapsed if the applicant fails to take any of the actions listed in proposed 314.110(b) and 601.3(b).*

*We recommend that the Agency notify the applicant prior to deeming an application withdrawn after 1 year if the applicant fails to take any of the actions listed in proposed*

*314.110(b). The withdrawal of an application should not be automatic until the sponsor has been notified and given reasonable time to respond.*

**Consistency between NDA, ANDA, and BLA Regulations**

While many changes are proposed to 21 CFR 314.110, *Complete Response Letter to Applicant*, only select changes are proposed to the companion biologics regulations at 21 CFR 601.3. For example, the Agency defines *resubmission* in the context of a CR letter in 314.110, but does not include this definition in the analogous BLA regulation at 601.3. Another example is described above under **Responses to CR Letters** where NDA/ANDA applicants are given 3 options following receipt of a CR letter while BLA applicants are given only 2 options.

*Comment: We recommend that the Agency revise the biologics regulations at 21 CFR 601.3 to include the topics contained in the corresponding drug products regulations or explain the brevity of the biologics regulations.*

We welcome the opportunity to comment on this Proposed Rule and, if appropriate, to meet with you to discuss these issues. Please feel free to contact me at (301) 941-1403.

Sincerely,



Lauren M. Hetrick  
Director, Global Regulatory Policy