



Date: OCT 14 2004

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

Re: Docket No. 2004N-0267

Response to FDA Call for Comments
Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications

Dear Sir or Madam:

Reference is made to the Federal Register Publication dated July 20, 2004, which described proposed rule changes to the regulations for new drug applications (NDA) and abbreviated new drug applications (ANDAs) for approval to market new drugs and generic drugs.

AstraZeneca has reviewed the proposed changes to 21 CFR Parts 312, 314, 600 and 601 and has identified areas in the proposed regulations that we believe would benefit from further Agency clarification. For convenience, the specific sections of the proposed rule have been identified and are then followed immediately by AstraZeneca comments and recommendations.

Please direct any questions or requests for additional information to me, at 302-886-5895.

Sincerely,

Barry Sickels
Executive Director
Regulatory Affairs
Telephone: (302) 886-5895
Fax: (302) 886-2822

2004N-0267
Enclosure

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

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Comments from AstraZeneca to FDA Proposed Changes to 21 CFR Parts 312, 314, 600 and 601 - Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications

[HHS Docket No. 2004N-0267]

For clarity the original proposed language is provided, with the use of underlined text to indicate the specific areas highlighted for AstraZeneca's comments.

1. Proposed language under 314.110(c) states that if the Agency determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, we might issue a complete response letter without first conducting required inspections and /or reviewing proposed product labeling.

Comment: The use of “we might” adds ambiguity to the Agency actions. When the determination of inadequacy is reached during the first half of the review cycle, it may be acceptable for the Agency to reserve the right to issue a complete response letter without first conducting required inspections and /or reviewing proposed product labeling. However, a complete response letter received toward the end of the review cycle would be expected to be complete, i.e., all components of the NDA thoroughly evaluated and addressed. By leaving the final decision, on whether the required inspections or the labeling review occur prior to issuing the complete response letter, to the Review Divisions or Review teams the Agency will be unintentionally encouraging the creation of dissimilar course of actions.

Recommendation: To modify the proposed language under 314.110(c) to state that if the Agency determine **early in the review cycle (or within the first half of the review cycle)**, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, we might issue a complete response letter without first conducting required inspections and /or reviewing proposed product labeling

2. Proposed language for 314.50(d)(5)(vi)(b), replace the requirement to submit a safety update report following a receipt of an approvable letter with a requirement to submit a safety report in a resubmission following receipt of a complete response letter.

Comment: It is reasonable to expect that in most cases a sponsor would receive the complete response letter toward the end of the first review cycle and that this will normally be well after a traditional 4-Month Safety Update has been submitted. Therefore, the amount of data that may be needed in the additional safety report could be substantial if there are many ongoing studies.

Recommendation: It will be helpful to applicants if the Agency include in the preamble to the regulations general guidance regarding whether there would be any difference in expectations on the content of the safety update to be provided in the resubmission that follows the complete response letter.

3. Proposed language under 314.60(b)(2) states that the submission of a major amendment to an original application, efficacy supplement, or resubmission of an application or efficacy supplement more than 3 months before the end of the initial review cycle will not extend the review cycle. However, the proposed regulations states that the Agency may, at their discretion, review such an amendment during the first review cycle or defer review until the subsequent review cycle

Comment: AstraZeneca believes that the proposed language under 314.60(b)(2) will have the unintended effect of widening the differences in interpretation that currently exist amongst Review Divisions regarding when a major amendment, submitted more than 3 months before the end of the initial review cycle, is reviewed or postponed to a subsequent review cycle. The current language also seems to discourage the possibility of a dialogue between applicants and Reviewing Divisions, during which the merits of the submission of a major amendment might be discussed and agreed in advance.

Recommendation: AstraZeneca requests that clarification be added to the regulations to provide guidance regarding what general criteria would normally be followed by the Agency in determining when a major amendment submitted more than 3 months before the end of the initial review cycle is reviewed during the initial review cycle.

4. Proposed language under 314.60(b)(3) state that a submission of a minor amendment to an original application, efficacy supplement or resubmission of an application or efficacy supplement will not extend the initial review cycle. However, it further states that the Agency may, at their discretion review such an amendment during the initial review cycle or defer review until the subsequent review cycle.

Comment: AstraZeneca believes that the proposed language under 314.60 (b)(3) will have the unintended effect of widening the differences that currently exist amongst Review Divisions in their interpretation of when a minor amendment submitted during the initial review cycle is reviewed or postponed to a subsequent review cycle. The current language also seems contrary to the language in 314.102(b), which encourages reviewers to communicate promptly to applicants easily correctable deficiencies found in the application or an abbreviated application when those deficiencies are discovered. The intent of 314.102(b) is to provide applicants an opportunity to correct any minor deficiencies and to submit pertinent amendments before the review period has elapsed. Therefore, the proposed language minimizes the value of a dialogue between applicants and Review Divisions regarding easily correctable deficiencies in the initial application.

Recommendation: AstraZeneca requests that clarification be added to the regulations regarding the criteria to be followed to decide when to postpone the review of a minor amendment to a subsequent review cycle. For example, illustrative language could be added to indicate that if a minor amendment is submitted late in the initial review cycle (such as 1 or 2 months before the end of the initial review cycle) or if the minor amendment does not provide information that directly address easily correctable deficiencies found in the application as described under 314.102(b), the Agency could at their discretion postpone the review of these

minor amendments to a subsequent review, provided other major deficiencies in the original application prevent the approval of the application at the end of the initial review cycle.

5. Proposed language under 314.110(c) states that an applicant agrees to extend the review period under section 505(c)(1) of the act until the applicant takes any of the actions listed in proposed 314.100(b). It further states that the Agency may consider an NDA applicant's failure to take any of the actions listed in 314.100(b) within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application.

Comment: The current proposed language for 314.100(c) does not seem to take into account all potential scenarios that may exist as a result of a complete response letter. For example, depending on the deficiencies noted in the complete response letter, a sponsor may invest several months reaching agreements with the Agency on the additional work that would best address the deficiencies. Many more months could follow generating data from new studies (if required), which could very likely extend beyond one year the time required to generate appropriate responses to the Agency's complete response letter. Further, as the 314.110(a) requirement for NDA applicants to take action within 10 days of receipt of an approvable letter (complete response letter under proposed rule) will be deleted under proposed 314.110(b), it is not clear whether any of the sponsor's communication with the Agency regarding the sponsor's intent to resubmit or amend the application would cancel or postpone the 1-year timeframe. Therefore, an unintended result of the current proposed regulations could be a less than complete resubmission, if the applicant believes that they must resubmit within the stated 1-year timeframe to avoid an automatic withdrawal.

Recommendation: AstraZeneca requests that clarification be added to the regulations to indicate that additional time may be granted for the resubmission of an application if an applicant is diligently working to address all deficiencies noted in the complete response letter but requires more than one year to provide a complete resubmission. AstraZeneca proposes that the underlined language above be modified as follows: "The Agency may consider an NDA applicant's failure to take any of the actions listed in 314.100(b) within 1 year after receiving a complete response letter to be a request by the applicant to withdraw the application, **if the applicant has not communicated the intent to resubmit the application or abbreviated application, or if the applicant has not submitted evidence of progress being made toward the completion of necessary work needed to address all the deficiencies identified in the complete response letter.**"

6. Agency request for comments on whether it would be appropriate for FDA to disclose the existence of an NDA or ANDA following issuance of a complete response letter and if so, what conditions, if any, should be placed on such disclosure.

Recommendation: AstraZeneca recommends that no changes be made to the current Agency policy regarding the disclosure of the existence of an application or abbreviated application. If the existence of an application or abbreviated application has not been publicly disclosed, the

Agency should continue its practice of acknowledging the existence of an NDA application only after issuing a tentative approval letter or an approval letter.