

**Apotex Inc. Comments re:
Applications for Approval to Market a New Drug;
Complete Response Letter; Amendments to Unapproved Applications**

**Food and Drug Administration
Proposed Rule Docket No. 2004N-0267**

Section II.A: Complete Response Letters

We have no objection to the use of Complete Response letters instead of Approvable and Not Approvable letters. However, in this section the proposed rule indicates that a complete response letter may be issued without first conducting required inspections and/or reviewing proposed labeling. While we do not object to this under the circumstances described, we recommend that the status of each review stream (labeling, chemistry and manufacturing, microbiology, bioequivalence and/or clinical reviews and inspection status) be clearly and explicitly stated within the complete action letter, in order to avoid any possible confusion about the application status.

II.B. Resubmissions

We do not object to the proposal to codify current FDA practice to start a new 6-month review cycle following receipt of a “major” resubmission in response to a complete action letter.

We are in strong opposition to the proposal to extend the review cycle for “minor” amendments to “an unspecified length of time”, for the following reasons:

1. The absence of a specific target for the review of a minor resubmission of an ANDA seriously hinders an applicant’s ability to predict the approval date of the application and, therefore, can result in substantial commercial disadvantage for a generic manufacturer. The timing of a generic manufacturer’s activities in preparation for a product launch is greatly dependent on a transparent regulatory review process that allows generic sponsors to predict application approval dates with as much accuracy as possible. Any delay in the onset of launch preparation as the result of an unpredictable approval date can severely harm a manufacturer’s ability to launch a product on time, causing substantial and irreparable financial losses as a result. Economic impacts may also be felt by patients and healthcare institutions due to delayed entry of low-cost generic alternatives to brand name drugs.
2. Without a specific target for the completion of the review of a minor resubmission, an applicant will be forced to follow-up with the FDA continuously over the course of the review cycle to ensure they have current information about the review status. This is contrary to the Office of Generic Drugs’ requests for applicants to follow-up on review status only at the provided target and not before, and creates a greater burden for both the applicant and the agency.

3. The review cycle of “an unspecified length of time”, as defined in the proposed rule as “from 30 days to a few months”, is contrary to previous revisions made in the guidance *Major, Minor and Telephone Amendments to Abbreviated New Drug Applications (December 2001)*, wherein the criteria for the classification of an amendment were revised to result in more minor amendments and fewer major amendments with the goal to “help in moving applications through the approval process more quickly...thus the total time for approval of ANDAs (would) be reduced”. However, the increase in the number of minors being issued appears to have resulted in longer review times of minor resubmissions, thus extending the overall review times of ANDAs. With the proposal that a minor resubmission may take “an unspecified length of time” to review, and without a definition of “a few months” (which can presumably extend to as many as 6 months), FDA performance standards, in the context of the review cycle, would be effectively reduced by as much as 50% or more. In addition, the distinction between a major and a minor amendment would become severely blurred.
4. Section II.B of the proposed rule states “These proposed changes with respect to NDAs are consistent with our user fee performance goals for resubmissions of human drug applications following receipt of an action letter. The proposed revisions for ANDAs are similar, although not identical, to those for NDAs”.

We do not find the revisions for NDAs and ANDAs to be similar, in that i) an NDA sponsor has the benefit of a specific timeframe within which all classes of resubmissions will be reviewed; ii) a Class 1 resubmission starts a 2-month review cycle; and iii) information about what constitutes a specific class of submission is provided (e.g., Class 1 resubmission is clearly defined as one “that contains 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, and other comparatively minor information”).

In contrast, i) an ANDA sponsor is given an unspecified timeframe for the review of a minor amendment; ii) the review can take as long as a few (potentially six) months; and iii) although a minor amendment is classified by the type of deficiencies exemplified in the guidance *Major, Minor and Telephone Amendments to Abbreviated New Drug Applications* (e.g., deficiencies in the Drug Master File, problems regarding GMPs, incomplete dissolution data and labeling deficiencies), the proposed rule indicates that the review time will vary based on criteria as ambiguous as “depending on the issues involved” or “depending on the contents of the resubmission”.

It appears that user fee performance goals, while “dedicated to expediting the drug development process and the process for the review of human drug applications”, are being implemented at the expense of generic manufacturers by reducing the transparency of the review process and extending the review times for those generic applications with only minor deficiencies, ultimately causing potential delays in public access to low-cost generic drugs.

In response to the above concerns, we propose certain changes to the proposed rule, as follows:

1. "Minor" resubmissions in response to a complete response letter are reviewed within 30-60 days from receipt.
2. The Agency carefully assess the issuance and classification of all complete response letters to uphold the intent to reduce ANDA approval times as per the guidance *Major, Minor and Telephone Amendments to Abbreviated New Drug Applications*.
3. The Agency attempt to resolve more deficiencies via telephone, rather than within a complete action letter, to reduce the review burden on minor resubmissions.

We feel that the above proposal accomplishes the following:

- ?? Allows for more accurate prediction of ANDA approval dates, thus increasing the chances for timely and successful product launch resulting in earlier public access to generic drugs, and reduced potential for financial losses for generic applicants;
- ?? Does not increase the burden on applicants and the Office of Generic Drugs to continuously correspond on application status;
- ?? Maintains current performance standards and the intent of the guidance *Major, Minor and Telephone Amendments to Abbreviated New Drug Applications* to reduce ANDA approval times; and
- ?? Achieves a greater similarity between review practices applied to NDAs and ANDAs as stated in the proposed rule.

Section II.C: Amendments to Unapproved Applications

This section proposes "to make only minor revisions to the regulations on submitting amendments to unapproved ANDAs in 314.96. The proposed rule would clarify that an amendment to an ANDA submitted before the end of the initial review cycle that contains significant data or information could extend the initial review cycle by as many as 180 days".

We do not agree with this revision, for the following reasons:

1. The current regulation, 314.96, states that an amendment to an ANDA "constitutes an agreement between the FDA and the applicant to extend the review period only for the time necessary (emphasis added) to review the significant data or information and for no more than 180 days". It appears that the only proposed change to the regulation is the removal of the condition that the review will extend the cycle only for the time necessary to review the data. Once again, we do not feel that this change is in-line with the intent to reduce ANDA approval times, and only creates greater difficulty for the applicant in estimating review and approval times, both of which can lead to delays in the availability of generic drugs.

2. The proposed rule refers only to the submission of an amendment that “contains significant data or information”. No definition of “significant” is provided, and there is no provision for the submission of an amendment that contains data or information not considered “significant”.
3. As per the proposed rule, “The submission of a major amendment to an original NDA within 3 months of the end of the initial review cycle constitutes an agreement to extend the review cycle by 3 months.” and “the submission of a major amendment to an NDA more than 3 months before the close of the initial review cycle, or the submission of a minor amendment during the initial review cycle, would not extend the review cycle”. In addition, the “FDA might, at its discretion, review such an amendment during the initial review cycle or defer review until the subsequent review cycle” which, in the latter case, would allow for review of the amendment in parallel with a resubmission and have no impact on the initial review cycle.

In contrast, it appears that any amendment by a generic applicant submitted at any time during the initial review constitutes an agreement to extend the cycle by 6 months.

We believe that the standards applied to NDAs which take into consideration the timing and content of the amendment are fair and appropriate, and that a similar approach should be taken with ANDA applications. We recommended the text of 314.96 be replaced as follows:

“The submission of a major amendment to an original ANDA at any time within the initial review cycle constitutes an agreement between the FDA and the applicant to extend the cycle only by the time necessary to review the data, and for no more than 180 days. A major amendment is defined as any new or revised information or data that, if it were to be submitted post-approval, would be categorized as a Prior Approval Supplement as defined in 314.70(b).

The submission of a minor amendment to an original ANDA within 3 months of the end of the initial review cycle constitutes an agreement between the FDA and the applicant to extend the cycle by 30 to 60 days. The submission of a minor amendment more than 3 months before the close of the initial review cycle would not extend the review cycle. A minor amendment is defined as any new or revised information that, if it were to be submitted post-approval, would be categorized as a Changes Being Effectuated or Changes Being Effectuated in 30 Days supplement as defined in 314.70(c).”

We feel that the above proposal accomplishes the following:

- ?? Allows for more accurate prediction of ANDA approval dates, thus increasing the chances for timely and successful product launch resulting in earlier public access to generic drugs, and reduced potential for financial losses for generic applicants;
- ?? Does not increase the burden on applicants and the Office of Generic Drugs to continuously correspond on application status; and

?? Achieves a greater similarity between review practices applied to NDAs and ANDAs by taking into consideration the content and timing of the amendment, which we consider to be a fair and appropriate approach.

Section III.C.5: Public Disclosure of Existence of Applications

We have no objection to the proposed revision to 314.430(b) to allow for FDA disclosure of the existence of an NDA or ANDA after issuance of an approval letter or tentative approval letter. We are opposed to any alternative approach regarding disclosure of the existence of an application, including the example provided whereby disclosure would take place following issuance of a complete response letter. Such disclosure could be potentially harmful, particularly in the generic pharmaceutical sector, to any competitive advantage a sponsor may have in the race to product launch. In addition, as discussed in the proposed rule, the process of notification by the sponsor to the agency not to disclose the existence of the application creates potential for error and would be burdensome to both the applicant and the agency.