

Wyeth

Date: October 15, 2004.

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

**Re: Docket No. 2004N-0267: July 20, 2004 (69 FR 43351-43366)**

**Dear Sir/Madam:**

Wyeth Pharmaceuticals is submitting the following comments on the FDA's proposed rule entitled *Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications* (July 20, 2004).

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biopharmaceuticals, vaccines and over the counter medications.

While we recognize that FDA has an obligation to update the regulations to provide for use of *complete response* letters in accordance with commitments made in conjunction with the Prescription Drug User Fee Act (PDUFA), we have concerns with certain aspects of the proposed rule. Our comments are described below.

***Submission of Major Amendments within 3 Months of the End of Review Cycle***

In addition to codifying the PDUFA provision for extending the initial review cycle by 3 months when a "major" amendment is submitted to an original NDA or efficacy supplement within 3 months of the end of the cycle, FDA is also proposing to give itself the option to defer the review of the amendment to the subsequent cycle (proposed §314.60(b)(1)). We believe this latter aspect is arbitrary and not consistent with the intent of PDUFA.

It is recognized that there may be occasions when the information contained in a major amendment may be too voluminous and be submitted too late during the review cycle to be reviewed within the three-month extension. However, neither the proposed rule nor the preamble provides examples to describe the circumstances when it might be appropriate to defer the review. The purpose of the 3-month extension of the review clock was to give the Agency sufficient time to complete its review of the application, including any submitted amendments, and take action based on a full review of the complete application by the PDUFA goal date. In our view, the overwhelming majority of amendments are submitted in direct response to FDA requests for additional information or clarification. In most of these situations

2004N-0267

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it would be unreasonable to penalize applicants who have paid a user fee by deferring the review of information or data *that the Agency requested* until a subsequent review cycle. Of further note, early communication of any information/data requests in keeping with FDA's PDUFA commitment on Good Review Management Principles will ordinarily result in receipt of applicant responses earlier in the first review cycle, thus allowing FDA more time to complete its review of the application before or by the PDUFA goal date (with or without a 3-month extension to the review clock).

*Wyeth therefore requests that proposed §314.60(b)(1) be revised to state that the Agency shall make every effort to complete its review of the full application, including any amendments, by the user fee goal date. Review of information submitted in a major amendment should only be deferred when the amount of new information and timing of the submission are such that it could not possibly be reviewed within the current review cycle.*

### ***Submission of Major Amendments more than 3 Months before the end of Review Cycle***

Similarly, proposed §314.60(b)(2) provides that submission of a major amendment more than three months before the end of the review cycle will not extend the cycle, but that the FDA may also, at its discretion, defer review until a subsequent review cycle. Once again, absent any specific criteria for when such a deferral might be appropriate we believe the language permitting FDA to arbitrarily defer its review of the amendment until the next cycle is inappropriate. The PDUFA goals did not provide for a clock extension under such circumstances because it was deemed unnecessary when the major amendment was received more than three months in advance of the user fee goal date. As noted above, an applicant who has paid a user fee is entitled to a complete response identifying any additional information that may be needed for approval based on FDA's review of the full application (including any submitted amendments).

*Accordingly, Wyeth requests that proposed §314.60(b)(2) be revised to state that FDA will ordinarily make every effort to complete its review of the full application or efficacy supplement, including any amendments submitted more than 3 months before the end of the initial review cycle, by the PDUFA goal date.*

### ***Submission of an Amendment that is not a Major Amendment***

Proposed §314.60(b)(3) states that FDA may also defer review of an amendment that is not a major amendment until the subsequent review cycle. As noted above, absent any specific criteria describing when a deferral of the review might be appropriate, we believe the wording permitting FDA to arbitrarily defer its review is inappropriate and inconsistent with the PDUFA objectives. By their very nature, non-major amendments are less complex and require less time to review than a

major amendment. Therefore, there is even more reason to expect that such amendments will be routinely reviewed by FDA within the same review cycle.

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*Wyeth requests that proposed §314.60(b)(3) be revised to state that FDA will ordinarily review all non-major amendments submitted to the application by the PDUFA goal date. FDA should also explain the circumstances under which it might be appropriate to defer the review until the subsequent review cycle (e.g., if the amendment is submitted close to the end of the review cycle and could not contribute to an approval decision because of the existence of major deficiencies that could not possibly be satisfactorily addressed within the same review cycle).*

In addition, for clarity, we request that the term *major amendment* be defined in the regulations.

### ***Major Amendments to Support a New Indication***

Proposed §314.60(b)(5) states that a major amendment may not include data to support an indication for a use that was not included in the original application, supplement, or resubmission. We agree that in most cases it would be unfair to expect the Agency to meet the PDUFA goal date if a major amendment for a completely new indication is submitted in the middle of the review cycle. However, there are situations where FDA requests for additional data or safety updates could lead to expansion or modification of the indication(s) proposed in the initial application (e.g., submission of long term safety data that supports chronic use). In addition, there may be situations when there might be a significant public health reason to allow submission of a major amendment to support a new indication. We therefore suggest modifying the wording to allow exceptions when the data to support the new or expanded indication has either been requested by FDA, or submitted with the FDA's prior concurrence.

### ***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. This proposal is not logical in view of certain existing PDUFA goals. For example, under the current user fee performance goals FDA is to act on 90 percent of original manufacturing supplements requiring prior approval within 4 months of receipt. When a complete response letter is issued resulting in a resubmission, why then should the review time for the resubmission exceed that required for review of the complete original supplement by 2 full months? This is particularly questionable considering that many of these resubmissions need only include the necessary data to answer specific questions resulting from the initial review cycle, and do not require nearly as much time for review as the initial supplemental application.

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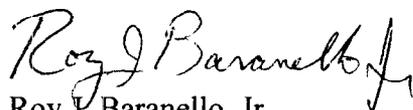
Wyeth recommends that proposed §314.110(b)(1)(iii) be re-worded to state that the length of the review cycle for the resubmission will not exceed that which was applicable for the original application. We further recommend that for prior-approval chemistry/manufacturing supplements FDA implement a type 1/type 2 classification scheme. 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.

***Consistency between Regulations for Drugs and Biologics***

Lastly, we question why the Agency is not proposing to codify the user fee review times for amendments and resubmissions for biologics, as well as for new drugs. We recommend that the biologics regulations in 21 CFR, Part 600 should also be updated to be consistent with the procedures and time frames for review of amendments and resubmissions of drug applications as proposed in Part 314.

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned proposed rule, and trusts that the Agency will take these comments into consideration.

Sincerely,



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Assistant Vice President,  
Worldwide Regulatory Affairs