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

Subject: **Docket No. 00D-0084**
Draft Guidance for Industry on Special Protocol Assessment

5 April 2000

Dear Sir/Madam:

Thank you for the opportunity to comment on the draft guidance entitled "Special Protocol Assessment" published in the Federal Register on February 9, 2000. Outlined below are Genzyme's comments for your consideration.

1. Section III(A)(1) specifies that a sponsor should notify the appropriate reviewing or applications division of an intent to request special protocol assessment by letter at least 30 days prior to submitting the request. No timeframe is specified for stability or clinical protocols, suggesting that FDA seeks advance notice of a request for protocol assessment only for carcinogenicity protocols. Please provide clarification.

2. How should letters detailing a sponsor's intention to request special protocol assessment be submitted? Should such letters be submitted as "Special Correspondence" and be accompanied by FDA Form 1571?

3. The recommendation to submit the protocol intended for special assessment at least 90 days before anticipated commencement of the study could add substantial time to the product development process, especially for those designated as "Fast Track". Genzyme recommends that protocols for "Fast Track" products submitted for special assessment be afforded priority review if such a review is requested in the cover memo. Genzyme recommends that FDA agrees to a 30 day review time frame under these circumstances.

4. Given that FDA has 30 says to review an IND submission, we ask that FDA respond to a request for special protocol assessment within 30 days, rather than the 45 days specified in the draft guidance.

5. Please provide further clarification regarding protocol changes. Does FDA make a distinction between major and minor changes?

   The language of "design, execution, and analyses" seems to imply Sponsor/Agency cohesion on the overall project scheme, rather than the details of protocol execution. Is it FDA's intent to review any and all changes to protocols submitted for special assessment? We would

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consider a substantive modification in the design, execution, and analyses to be a major change requiring FDA review. However, during product development, there may be many occasions where it is necessary to make minor changes to the protocol. Mandating sponsor notification and Agency review for such minor changes would seem to be an onerous and labor intensive burden for both parties, especially as sponsors may currently implement certain amendments as soon as IRB approval is obtained. Further, the guidance document states that changes to a protocol submitted for special assessment will result in a renewal of the 45 calendar day FDA review period. This time frame is reasonable for major alterations, but would cause significant delay in the product development process if any change to the protocol restarts the clock.

6. The guidance notes that a review division will not be bound by a documented special protocol assessment if the sponsor fails to follow the agreed upon protocol. Again, this raises the issue of major versus minor protocol changes. The Clinical Trial Final Report contains a listing of any protocol violations. Is it possible that the special protocol assessment agreement could be considered null and void based on a minor protocol violation? For example, what happens if a patient is assessed at a follow-up appointment one week out of the protocol specified window? Does this invalidate the documented special protocol assessment? There seems to be a clear distinction between a protocol violation of this nature and a one where the inclusion/exclusion criteria were disregarded.

7. Section IV (A) explains that the reviewing or application division evaluates written requests for special protocol assessment to determine if the submission is appropriate for such assessment. If the division concludes that the assessment is inappropriate, " . . . the division should notify the sponsor of the reasons for the determinations as soon as possible after the Agency's receipt of the request." We believe that it would be beneficial to sponsors to know immediately if the Agency is planning to decline a request for assessment and recommend a deadline for this initial appraisal. Perhaps a time frame of five business days would be appropriate, with the understanding that the Agency would follow with a documented rationale as soon as possible.

8. This guidance uses the terms "efficacy" and "effectiveness" interchangeably throughout the document.. These words can have different meanings depending on the context. Please define these words or confirm that they have identical definitions within the context of this guidance document.

Genzyme appreciates the opportunity to comment on this draft guidance. Please contact me at (617) 252-7757 or Juliette Shih at (617) 761-8929 should you have any questions regarding this letter.

Cordially,

Alison Lawton
Senior Vice President
Regulatory Affairs

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