

April 7, 2000

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

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RE: Docket No. 00D-0084
Draft Guidance for Industry - Special Protocol Assessment

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 \$2 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. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

As a leading and innovative pharmaceutical firm, Merck has frequently requested and been granted face-to-face meetings with both CDER and CBER to review pivotal trials that were central to development of a mutually beneficial Package Circular. We are, therefore, interested in the draft Guidance for Industry - Special Protocol Assessment and believe that we are well qualified to comment on it constructively.

We commend FDA for the effort to issue a Guidance document that will enhance communication between the FDA and sponsors, ensuring that adequate and accurate guidance is provided for these pivotal steps in successful development of a new pharmaceutical product. In general, Merck supports the rationale and content of the proposed Guidance. However, Merck has concerns about specific portions of this policy as written. Specific recommendations are made with this communication that will address our concerns, and which would enhance the concept of the assessment of special protocols.

POINTS OF CONCERN

1. Written Documentation

The clear purpose of the draft Guidance is to develop an agreement between the FDA and sponsors over the nature of the protocol and the data that need to be collected. The draft Guidance clearly articulates that all agreements and disagreements are to be documented in a written communication sent from FDA to the sponsor. However, the laudable

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purpose of the draft Guidance is subverted by the sentence: "Absence of an articulated disagreement on a particular issue may not be assumed to represent an agreement reached on that issue" (lines 46-48). It is reasonable that a sponsor will assume that in the absence of any advance comments from the FDA, the desired outcome will be achieved upon successful completion of the protocol. The phrase quoted above provides the FDA with an option of claiming at a later date that successful execution of the protocol may not lead to the desired outcome on the basis of a reason that was never articulated to the sponsor. Merck feels very strongly that this phrase should be deleted from the draft Guideline in its' entirety.

While the draft Guidance document specifies that agreements and disagreements will be documented, there is no timeline for doing so. This omission is surprising in light of the clear timelines presented for other aspects of the Special Protocol Assessment. It is particularly important that disagreements be documented in a timely manner so that a sponsor can develop a response or modify the protocol, as appropriate. We suggest that written documentation of disagreements be provided to sponsor within 45 days after it is determined that the FDA and sponsor do not agree, by which time the reasons for the disagreement will be clear.

2. Carcinogenicity Protocols Eligible for Special Assessment

Unlike the stability protocols and clinical protocols, the draft Guidance specifies that background information on carcinogenicity protocols be provided at least 30 days in advance of submitting a request. Effectively, this increases the FDA review from 45 days (as per stability and clinical protocols) to 75 days. The standards for all special protocols should be identical, without requiring provision of additional information for carcinogenicity protocols prior to protocol submission itself.

3. Stability Protocols Eligible for Special Assessment

The text of the draft Guideline specifies that stability protocols that are "significantly different from the standard stability protocol" may be considered for Special Assessment (lines 84-85). The terms "significantly" and "standard" are ambiguous and should be clarified. We recommend replacing the phrase "significantly different from the standard stability protocol" to "that differs from stability protocols specified by ICH Q1A(R) (Stability Testing of New Drugs and Products-Revised)".

The FDA correctly notes that it is critical to ensure that "process described in the request for an assessment of the stability protocol will not differ substantively from the process used for marketed material" (lines 89-92). While we endorse this position, we recommend that the term "differ substantively" be more clearly defined as having the potential to introduce new impurities.

In discussing the content of a stability protocol that could be submitted, the draft guideline requests that a sponsor provide "relevant" manufacturing data (line 148). The term "relevant" is imprecise, and can be understood differently by a sponsor and the FDA. A misunderstanding on the nature and extent of data required for inclusion in a

special assessment Stability Protocol may lead to a refusal by the FDA to accept the protocol. To avoid such a situation, we recommend replacing the phrase "relevant manufacturing data" with "manufacturing data fully describing the process covered by the Stability Protocol."

Another item requested is for provision of the "the expected shelf-life" as a part of the Stability Protocol to be evaluated (lines 149-150). For the sake of greater clarity, we recommend that the term "expected shelf-life" be replaced with "shelf-life that is anticipated at the time of filing."

4. Clinical Protocols Eligible for Special Assessment

As currently written, the only clinical protocols that are eligible for special protocol assessment are phase 3 trials that will form the primary basis for an efficacy claim (lines 94-95). We acknowledge the utility of such discussions for pivotal efficacy studies, but the concept of special protocol assessments should also include any pivotal study that would lead to a new Package Circular claim and/or indication for a product.

5. Providing an Assessment without a Meeting

PDUFA goals stipulate that a meeting is recommended for an end-of-phase 2/pre-phase 3 meeting to review the clinical trial that will form the basis for an efficacy claim. However, we note the draft Guideline states that "if the Agency is already familiar with the development context of a proposed clinical trial and has an understanding of the questions that will be raised regarding the protocol, the Agency may provide a comprehensive assessment without requiring an end-of-phase 2/pre-phase 3 meeting" (lines 98-102). Merck is of the opinion that if the development context is clear, the FDA should be able to provide an assessment without requiring a meeting. Accordingly, we recommend that the phrase "may provide" be changed to "will provide".

6. Action on a Request

The draft Guideline provides clear guidance on the steps that will be followed if the FDA agrees to assess a Special Protocol. However, the draft Guidance provides only limited information on the procedural steps that will be followed in the event that the FDA decides that a submitted protocol is not appropriate for Special Protocol Assessment. The text, as written (lines 168-169), states that the FDA "should notify the sponsor of the reasons for the determination as soon as possible."

Given that the FDA has already performed an initial evaluation of the submitted protocol, the conclusions reached on the suitability of the protocol for special review should be communicated to sponsors. Accordingly, the phrase "should notify" should be changed to "will notify". In addition, there is no reason to delay provision of the FDA viewpoint that the submitted protocol is not appropriate for Special Protocol Assessment. We recommend that the phrase "as soon as possible" be modified to "no later than 30 days after receipt of the request for a special protocol assessment".

7. Procedure to be Followed When External Experts are Consulted

The draft Guideline specifies that there may be situations where the opinions of advisory committee members, special government employees, or other consultants may be sought. Merck supports this option because it provides an opportunity to bring in specialized expertise. However, we are concerned about the duration of time that will be taken to seek this advice. As currently written, the draft Guideline provides for an undefined period of time between the notification that the FDA is seeking an opinion of experts, and the actual meeting of the experts (lines 189-202). The FDA is strongly urged to define the maximum amount of time that will be given to organize a meeting of experts (e.g. 60 days after submission of a protocol for ad hoc meetings, or at the next scheduled meeting of the appropriate Advisory Committee).

In addition, we wish to clarify that if the guidance of an Advisory Committee meeting is sought, the meeting would be held in closed session and the members of the committee would not have conflicts of interest. Since the protocol is being reviewed prior to execution, and since disclosure of the proposed protocol may impact the financial status of the sponsor, it is not appropriate to review a special protocol in an open public forum.

SUMMARY

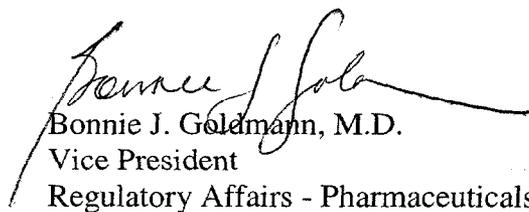
In conclusion, clearer timelines need to be established for written documentation of agreements and disagreements; for providing sponsor with the rationale why a submitted protocol may not be appropriate for consideration for Special Protocol Assessment; and for the scheduling of reviews by expert consultants. Furthermore, unless otherwise stated, sponsors should be able to assume that approved Special Protocols have the agreement of the FDA in all aspects. We also urge that the concept of Special Protocols be extended to all clinical trials that are pivotal for new claims or new indications. There should not be a requirement for provision of additional background information for carcinogenicity protocols prior to a request for a Special Protocol Assessment. Finally, we recommend modifying some of the terminology used in describing the applicability of Special Protocol Assessments to stability protocols.

We appreciate the opportunity to comment on the draft Guidance for Industry - Special Protocol Assessment and would welcome the opportunity to discuss it further.

Sincerely,



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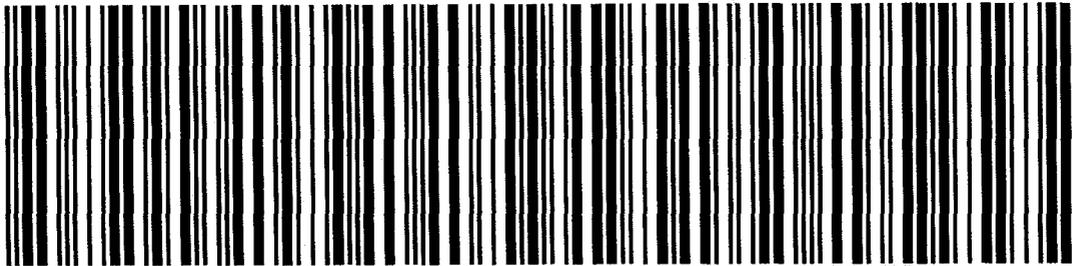
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