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ASSOCIATE VICE PRESIDENT
US REGULATORY AFFAIRS

PhRMA

April 10, 2000

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5600 Fishers Lane
rm. 1061
Rockville, MD 20852

Re: Docket No. 00D-0084; Draft Guidance for Industry on Special Protocol Assessment; 65 Federal Register 6377; February 9, 2000

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing medicines allowing patients to lead longer, happier, healthier and more productive lives. Investing \$26 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for new cures.

Our comments in this letter concern the Food and Drug Administration's (FDA) issuance of a draft guidance for industry entitled "Special Protocol Assessment." This draft guidance implements agreements on both clinical and non-clinical protocol assessments reached during negotiations between industry and the FDA regarding the reauthorization of the Prescription Drug User Fee Act (PDUFA) that took place in 1996. PDUFA was reauthorized as part of the Food and Drug Modernization Act of 1997 (FDAMA) and several of the PDUFA agreements were codified into law.

Section 119(a)(4)(c) of FDAMA directs FDA to handle agreements on clinical protocol design as follows:

Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

- “(i) with the written agreement of the sponsor or applicant; or*
- “(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.*

00D-0084

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PhRMA member companies believe that this provision will resolve many misunderstandings between the sponsor and the FDA and add a significant level of certainty to the clinical development process.

Specific details regarding the implementation of Special Protocol Assessments were outlined in a letter from Secretary of Health and Human Services, Donna Shalala to Senator James M. Jeffords, dated November 12, 1997. That letter, as noted in section II of this proposed guidance, states that "*protocols qualifying for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the primary basis of an efficacy claim.*" As per the negotiated agreement, the Agency is to provide a written response to the sponsor that includes a succinct assessment of the protocol and answers questions posed by the sponsor with 45 days of receipt of the proposed protocol.

Unfortunately, this proposed guidance negates the agreed upon time for reviewing carcinogenicity protocols. As published in section III.A.1 of the proposed guidance, the FDA states "*(the sponsor) should notify the director of the appropriate division of an intent to request a special protocol assessment by letter at least 30 days prior to submitting the request. With the notice of intent, the sponsor should submit relevant background information so that the Agency may review (or re-review) reference material related to carcinogenicity protocol design prior to receiving the carcinogenicity protocol.*" At best, implementation of this proposed language will lead to a double review of the appropriate information. More disturbing to PhRMA is that this 30 day notification unilaterally extends the review time frame for protocol assessment to 75 days.

The preamble to section III.A notes that a "*...special protocol assessment will not be provided after a study has begun.*" While this may be appropriate in some cases, there are other cases where it may be critical for the sponsor to get FDA's opinion, particularly for those studies of long duration where new information from interim analyses or from other trials may warrant modification of the study, or where the sponsor has started a study at risk and would consider altering or restarting the study based on FDA input. PhRMAs suggest striking this language.

Section IV.A states "*(If special protocol assessment is not appropriate (e.g., the protocol does not meet the criteria for special protocol assessment) the division should notify the sponsor of the reasons for the determination as soon as possible after the Agency's receipt of the request.*" PhRMA believes that FDA should respond to the sponsor within 15 days of submission if such a determination is made.

Section IV.B.1 states "*(T)he Agency will consider a request for special protocol assessment of a revised protocol to be a new request and will act on the revised protocol within 45 days.*" There may be some discussion of minor points in a submitted protocol

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that result in revision. Review of these points should not take an additional 45 days. Only unilateral and substantive revision by the sponsor should be considered a "complete" resubmission and warrant an additional 45 day review period.

Section IV.B.2 deals with potential use of an advisory committee to review a special protocol assessment. PhRMA hopes that any review of such a protocol by a full advisory committee meeting or consultants is a rare event. In general, FDA has sufficient in-house expertise to review these protocols. As the FDA is aware, many advisory committees meet quarterly. Scheduling reviews of protocols could delay the start of the study by as much as four months given the timing and the need to deliver materials to committee members, in advance of the committee meeting. In those few cases where the FDA needs additional assistance, it would be more prudent to seek advice from selected advisory committee members, outside consultants, or special Government employees in a timely manner.

In Section VI.A PhRMA believes that the FDA is too negative in asserting that "*the Agency will not necessarily agree that a specific finding (e.g., a particular p value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision.*" PhRMA can envision a number of well-defined situation where the Agency may agree that a specific finding could satisfy a specific objective or support an approval decision. One of the principal reasons for including Section 119 in FDAMA was to add a level of certainty to the drug development process.

PhRMA believes that two parts of Section B should be changed to read as follows:

1. Lines 234-38: "*Failure of a sponsor to follow the intent and objective of a protocol that was agreed upon with the Agency will be interpreted as the sponsor's understanding that the protocol assessment is no longer binding.*"
2. Lines 243-44: "*A clinical protocol assessment will no longer be considered binding if (1) the sponsor and FDA agree in writing to change the protocol, in which case the revised protocol becomes binding.*"

PhRMA trusts that these comments are of value to the FDA as this guidance is formalized.

Sincerely,

