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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 00D-0087; Draft Guidance for Industry on IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing, and Control Information; (65 Federal Register 5645) February 4, 2000

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over \$26 billion in 2000 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA members sponsor the majority of commercial Investigational New Drug Applications (INDs) submitted to the FDA. Our members, therefore, are vitally interested in the draft guidance and see it as another effort on the part of FDA to rationalize and streamline the IND submittal, evaluation and review process. FDA's efforts in this regard were initiated with the November, 1995 Guidance for Industry on the Content and Format of INDs for Phase 1 Studies of Drugs, including Well-Characterized Therapeutic, Biotechnology-Derived Products. This was followed by the February, 1999 Draft Guidance for Industry for INDs for Phase 2 and 3 Studies of Drugs, including Specified Therapeutic Biotechnology-Derived Products. FDA has also explored this issue in other guidances relating to this topic and guidances for meetings with FDA during the various phases of drug development to discuss Chemistry, Manufacturing and Controls information applicable to specific IND applications.

Within that context, our members have evaluated the draft guidance and developed general and specific comments that are intended to assist the FDA in the preparation of a final guidance that reflects all of the FDA's efforts toward streamlining the IND process. This will provide both the industry sponsors and the FDA optimum efficiency in meeting their mutual responsibilities for protecting study subjects.

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General Comments:

1. Historically, joint Clinical / CMC meetings with the Agency do not allow for adequate time to address all Clinical and CMC issues.

FDA and Sponsor meetings at key development milestones are critical to the timely and effective development and approval of new drug products. These meetings support effective communication and resolution of issues throughout the development process. The three proposed meetings (pre-IND, EOP2, and pre-NDA/BLA) are appropriate standard meeting times to discuss CMC development issues and plans to support the next phase of clinical development or drug registration. This draft guidance identifies key CMC topics that may require discussion at these meetings. However, the suggested use of multidisciplinary (clinical and CMC) meetings could preclude the participants' ability to adequately discuss and reach agreement on both clinical and CMC plans during the scheduled meeting time. Frequently, insufficient time remains at the end of these joint meetings, necessitating an additional meeting.

To allow focused discussion and resolution of CMC and clinical issues, PhRMA recommends that separate CMC-specific meetings outlined under section II D.2. "Format of Meeting: CMC-Specific Meeting" (line 76 and following) should be the norm, especially for the EOP2 and pre-NDA/BLA meetings. EOP2 and pre-NDA/BLA meetings discuss detailed CMC strategies for Phase 3 clinical supplies, registration data generation, commercial process scale-up and validation efforts and content/format of the NDA. Additionally, co-development partnerships between companies warrant separate clinical and CMC IND meetings to limit the scope of discussions, for confidentiality reasons, based on representatives present. PhRMA agrees that CMC-specific meetings should be scheduled immediately prior to or after the clinical-specific meeting, wherever possible (reference Section IV. B lines 160 – 163).

The Agency companion draft guidance, entitled "Formal Meetings with Sponsors and Applicants for PDUFA Products," (Dated February 2000) indicates that pre-IND, certain EOP1, EOP2, and pre-NDA/BLA meetings are Type B meetings. This guidance further states that "FDA expects generally to grant only **one of each** of the Type B meetings for each potential application..." for a potential of 4 separate Type B meetings (see Section II. B. Type B Meetings). Previously, the Agency has allowed additional CMC-specific meetings not linked to typical development milestones. These meetings are generally required to obtain Agency input on unexpected issues or changes in CMC development strategy. PhRMA recommends that the guidance be revised to clearly indicate that additional CMC specific meetings will be granted, if warranted, based on information or issues that affect previously agreed upon strategies.

2. **In order to assure that these meetings are productive and address all the concerns of both the Sponsor and the Agency, the agenda topics and list of questions to be discussed need to be agreed to prior to the meeting. Additional topics should not be raised for the first time at these meetings.**

The sponsor is required to prepare and submit a pre-meeting package summarizing available CMC information and a complete list of CMC-related questions to be covered during the meeting. In order for the meetings to be productive, the discussions should be limited to these topics and questions. However, lines 84 – 87 indicate that “the Agency may also wish to discuss relevant questions on safety issues or various scientific and/or regulatory aspects of the drug” based on their review. These additional topics or questions from the Agency should be communicated to the sponsor at least 72 hours before the meeting. This will allow the Sponsor to assure that the appropriate company representative(s) and information are available at the meeting to adequately address the additional concerns. To allow adequate Agency review time, the PDUFA Meeting guidance requires the Sponsor to submit the pre-meeting package for Type B meetings, including the agenda and discussion topics, at least 4 weeks before the meeting. Likewise, the Sponsor should have adequate time (72 hours before the meeting) to prepare relevant information to address any additional topics identified during FDA review of the pre-meeting package.

3. **The guidance needs to address the topic of inter-division and/or inter-center review agreements at each of the three proposed meetings.**

Drug products with multiple indications across multiple review divisions or drugs that require an inter-center review agreement (i.e., combination drug/device product, ... etc.) require early agreement on a coordinated IND and NDA/BLA review strategy. Prior to the pre-IND meeting, the appropriate Agency divisions/centers should meet and agree upon the review strategy for products in this category. During the pre-IND meeting, the Agency should outline its coordinated CMC review strategy for the IND and NDA, indicating the designated lead review division, any requirements for cross referencing to the other divisions and/or centers, and the Agency’s main contact for the coordination of meeting requests. Additionally, it is critical that the Agency feedback received by the Sponsor at each IND meeting is representative of the combined expectations of the divisions/centers responsible for the review and approval of the drug product. PhRMA recommends that this guidance list this as a potential topic for discussion at each IND meeting.

4. The guidance needs further clarification regarding the intent of examples described as Sponsors “Approach to ” validation or specifications under EOP2 meetings.

Some of the examples include discussion of the sponsor’s “approach” in certain areas [i.e., specifications (lines 179 – 180) and sterilization process validation (lines 192 – 193) during EOP2]. While the discussion of the sponsor’s “approach” in these areas are appropriate during an EOP2 meeting, PhRMA notes that this should not become an expectation that final specifications or the final protocols are available during this meeting. Actual validation protocols are not required to be completed at this stage.

5. The draft guidance is unclear whether the three described meetings (i.e., pre-IND, EOP2, and pre-NDA) are mandatory for all INDs.

New drug development programs that are without significant issues, that meet published FDA guidances or that are similar to previous sponsor development experiences may not benefit from one or more of the three meetings discussed in the guidance. In these cases, the Sponsor would submit a general CMC summary with the clinical meeting information package indicating no CMC-related issues require discussion. If the Agency identifies CMC questions after reviewing the pre-meeting package, they could ask the sponsor to present additional information either before or during the meeting to address the question (see General Comment #2 above). This would avoid unnecessary Sponsor participant travel expenses and meeting time for both the Agency and Sponsor. PhRMA recommends that the guidance indicate that these three meetings are generally intended, but not always required (i.e., not mandatory) to discuss and resolve any outstanding CMC development and submission issues.

Specific comments on the draft guidance keyed to specific line numbers/issues in the guidance are provided in the attached compilation.

PhRMA appreciates the opportunity to evaluate and comment upon the FDA draft guidance for this important topic. As noted in our previous submissions to the Docket and in other communications relating to IND CMC documentation guidances, PhRMA’s technical experts would welcome further opportunities to meet with FDA to discuss the issues raised and to further assist the Agency in the preparation of a final guidance.

Sincerely



Thomas X. White

Attachment

Specific Comments:

Line	Issue or Guidance Text	Revised Text Changes are highlighted in red.	Rationale & References
I. INTRODUCTION			
9 – 11	These meetings can address questions and scientific issues that arise during the course of a clinical investigation, aid in the resolution of problems, and facilitate evaluation of drugs.	These meetings are available at the request of the Sponsor to can address outstanding questions and scientific issues that arise during the course of a clinical investigation, aid in the resolution of problems, and facilitate evaluation of drugs.	Clarify that these meetings are not mandatory. New drug development programs without significant issues, meeting published FDA guidances or that are similar to previous sponsor development experiences may not benefit from one or more of the three meetings discussed in this guidance. This would avoid unnecessary Sponsor participant travel expenses and meeting time for both the Agency and Sponsor. (Also see changes to line 34 below)
12	Insert following	“... and/or regulatory process. However, additional meetings may be scheduled at times other than those described herein to address unexpected changes in the CMC development plan. This guidance is intended to assist in making ...”.	Allow for additional CMC meetings that are necessary to address CMC issues that arise during development.

Line	Issue or Guidance Text	Revised Text Changes are highlighted in red.	Rationale & References
II. GENERAL ASPECTS: A. Purpose of Meeting			
29 – 31	The general aspects of meetings provided in this guidance summarize the information provided in the formal meetings and fast track drug development guidances listed in section I and supplement this information with respect to CMC.	The general aspects of meetings provided in this guidance summarize the information <u>required for Type B meetings discussed</u> in the formal meetings and fast track drug development guidances listed in section I and supplement this information with respect to CMC.	Clarify that these meetings are Type B meetings as defined in Agency draft guidance entitled “Formal Meetings with Sponsors and Applicants for PDUFA Products” (Dated February 2000).
34	Insert following	“... varies with the phase of the investigation study. The three meetings described herein are recommended, but are not mandatory for CMC discussions. In such cases, the clinical information package will also contain a summary of the available CMC information and the updated development plan. The Sponsor should indicate in the information package that it believes no CMC discussions are required at this time. For pre-IND meetings...”	Clarify that the three specific meetings are not mandatory for CMC discussions. The sponsor will provide the rationale for this determination and FDA will have the opportunity to request that additional information and/or CMC representatives be available at the clinical meeting to address FDA concerns. (See comment for line 90 below).

Line	Issue or Guidance Text	Revised Text Changes are highlighted in red.	Rationale & References
II. GENERAL ASPECTS: E. Focus of Meeting			
90	Insert following	“... dosing frequency, or duration. The Agency will notify the Sponsor at least 72 hours prior to the meeting of any additional topics not on the agenda and/or list of CMC questions provided by the Sponsor.”	This will allow the Sponsor to assure that the appropriate company representative(s) and information are available at the meeting to adequately address the additional concerns. The FDA is given 4 weeks review time, which should allow adequate time to complete its review and supply the additional comments to the Sponsor at least 72 hours prior to the meeting.
III. PRE-IND MEETING: C. Focus of Meeting			
119	Insert following:	· Inter-division and/or inter-center agreements: designated of lead division review and submission requirements	Emphasize early discussion and agreement on inter-division and/or inter-center review agreements.
IV. END OF PHASE 2 MEETING: C. Focus of Meeting			
194	Insert following:	· Discuss any changes in development strategy and potential impact on inter-division and/or inter-center agreements	Emphasize continued discussion of inter-division and/or inter-center review agreements throughout product development and determine impact of changes in the development strategy.
180	Insert following:	· Approach to specifications (i.e., tests, analytical procedures, and acceptance criteria, if established)	Clarify that acceptance criteria may still be “To Be Monitored” at EOP2. The Agency currently accepts that not all tests have established specifications at EOP2.

Line	Issue or Guidance Text	Revised Text Changes are highlighted in red.	Rationale & References
193	Insert following:	· Approach to sterilization process validation and/or container closure challenge testing, where applicable (Note: Actual validation protocols are not required to be completed at this stage)	Clarify that an outline of the validation approach is all that is required at this stage. The Agency currently accepts the fact that final validation protocols are not always available at this time.

V. PRE-NDA or PRE-BLA MEETING: B. Meeting Request, Information Package, and Format			
243	Insert following:	<p>“... and format for the meeting. A multidisciplinary or separate CMC-specific pre-NDA or pre-BLA meeting may be held. If a CMC-specific meeting is held, it is preferred that it be scheduled to take place immediately prior to or after the meeting on clinical issues. Under appropriate circumstances, multiple CMC-specific meetings may be required. A pre-NDA or pre-BLA meeting should be held at least 6 months prior to the planned NDA or BLA submission date, or earlier if new CMC issues and or major changes in information discussed in previous meetings will be presented.”</p>	<p>Specify that CMC-specific meetings are appropriate for pre-NDA or pre-BLA meetings and that multiple pre-submission meetings are sometimes required and have been accepted by the Agency in the past.</p>
268	Insert following:	<p>· Discuss any changes in development strategy and potential impact on inter-division and/or inter-center agreements</p>	<p>Emphasize continued discussion of inter-division and/or inter-center review agreements throughout product development and determine impact of changes in the development strategy.</p>