



**Lilly Research Laboratories**  
A Division of Eli Lilly and Company

Lilly Corporate Center  
Indianapolis, Indiana 46285  
317.276.2000

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May 1, 2000

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

Re: [Docket No. 00D-0087] IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information. (Published in Federal Register: February 1, 2000)

Dear Madam or Sir:

Eli Lilly and Company is pleased to have the opportunity to provide comments on the Draft Guidance for Industry on IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing and Controls Information.

We agree with FDA on the importance of IND meetings to discuss the sponsor's CMC strategies for the development and ultimate registration of new drug products. Historically, these CMC meetings promoted constructive dialogue and agreement on regulatory requirements and strategies throughout the product development.

Attached please find our comments on the draft guidance. The attachment includes general comments as well as comments about specific sections in the guidance where Lilly believes further clarification is warranted. We hope that these comments will result in revisions in the guidance that reflect our past experience with the agency.

Please feel free to contact me at (317) 276-0368 for clarification of any comments.

Sincerely,

Tobias Massa, Ph.D.  
Executive Director, Global Regulatory Affairs

00D-0087

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**Draft Guidance for Industry on  
IND Meetings for Human Drugs and Biologics;  
Chemistry, Manufacturing, and Controls Information**

Published in Federal Register: February 1, 2000  
Docket No. 00D-0087

**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 This draft guidance identifies key CMC topics that may require discussion at these meetings.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 jeopardize 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 and necessitates an additional meeting.

To allow focused discussions and resolution of CMC and clinical issues, 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. It is agreed that CMC-specific meeting 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 are generally required to obtain Agency input on unexpected issues or changes in CMC development strategy. The guidance should 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 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 require 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 information to address any additional Agency topics identified during 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 at each IND meeting is representative of the combined expectations of the divisions / centers responsible for the review and approval of the drug product. This guidance should list this as a potential topic for discussion at each IND meeting.

**4. The guidance needs further clarification regarding 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]. Whereas the discussion of the sponsor’s “approach” in these areas are appropriate during an EOP2 meeting, 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 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 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 request 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. The guidance should indicate that these three meetings are suggested (not mandatory) to discuss and resolve any outstanding CMC development and submission issues.

| Line  | Issue or Guidance Text | Revised Text<br>Changes are highlighted in red.  | Rationale & References   |
|---|------------------------|--|--|
|   |                        | information package that it believes no CMC discussions are required at this time. For pre-IND meetings...”  |  |
| <b>II. GENERAL ASPECTS: E. Focus of Meeting</b>   |                        |  |  |
| 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 the appropriate company representative(s) and information are available at the meeting to adequately address the additional concerns. 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. |
| <b>III. PRE-IND MEETING: C. Focus of Meeting</b>  |                        |  |  |
| 119   | Insert following:      | <ul style="list-style-type: none"> <li>• Inter-division and/or inter-center agreements: designation of lead division review and submission requirements</li> </ul>   | Emphasize early discussion and agreement on inter-division and/or inter-center review agreements.  |
| <b>IV. END OF PHASE 2 MEETING: C. Focus of Meeting</b>                                    |                        |  |  |
| 194   | Insert following:      | <ul style="list-style-type: none"> <li>• Discuss any changes in development strategy and potential impact on inter-division and/or inter-center agreements</li> </ul>  | Emphasize continued discussion of inter-division and/or inter-center review agreements throughout product development and determine impact of changes in the development strategy.   |
| 179 – 180   | Insert following:      | <ul style="list-style-type: none"> <li>• Approach to specifications (i.e. tests, analytical procedures, and acceptance criteria, if established)</li> </ul>  | 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.  |
| 192 – 193   | Insert following:      | <ul style="list-style-type: none"> <li>• 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)</li> </ul> | 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.   |
| <b>V. PRE-NDA or PRE-BLA MEETING: B. Meeting Request, Information Package, and Format</b> |                        |  |  |

| Line | Issue or Guidance Text | Revised Text<br>Changes are highlighted in red.  | Rationale & References  |
|------|------------------------|--|---|
| 245  | 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> | Specify that CMC-specific meetings are appropriate for pre-NDA or pre-BLA meetings and that multiple. Also noted that multiple pre-submission meetings are sometimes required and have been accepted by the Agency in the past. |
| 266  | Insert following:      | <ul style="list-style-type: none"> <li>• Discuss any changes in development strategy and potential impact on inter-division and/or inter-center agreements</li> </ul>  | Emphasize continued discussion of inter-division and/or inter-center review agreements throughout product development and determine impact of changes in the development strategy.  |

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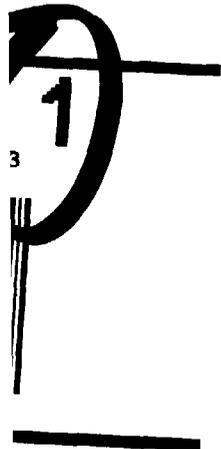
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