

CONCEPT PAPER

End-Of-Phase-2A Meetings With Sponsors Regarding Exposure-Response of IND and NDA Products (Draft 10/16/2003)

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

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Procedural**

Table of Contents

- I. Introduction.....
- II. Objectives of the Meetings.....
- III. Two-Year Pilot Program.....
- IV. Procedure for Requesting the Meetings.....
- V. Information Package.....
- VI. Procedure for Conducting the Meetings.....
- VII. Documentation.....

I. Introduction

This document is intended to provide guidance to industry on policies and procedures adopted by the Center for Drug Evaluation and Research (CDER) for scheduling and conducting formal meetings between CDER staff and sponsors regarding regulatory issues related to exposure-response of IND or NDA products.

FDA published a guidance for industry on “Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications” in April 2003. The guidance describes the use of exposure-response information for drug developments and regulatory decisions. Many recent NDA examples illustrated the critical role of exposure-response studies in supporting efficacy and safety of drugs and dose selection for patients. Some of these examples have been presented at the FDA Clinical Pharmacology Sub-Committee Advisory Meeting (Nov. 17/18 2003) and can be found on the FDA website (<http://www.fda.gov/cder/audiences/acspage/acslst1.htm>). The examples suggest that phase 2 exposure-response data can provide information that might decrease the uncertainty of further drug development. These NDA examples raise the possibility that early sponsor-FDA meetings to discuss exposure-response issues would facilitate the drug development process and reduce the regulatory review cycles.

II. Objectives of the Meetings

Food and Drug Administration (FDA) initiatives are directed at identifying opportunities to make innovative medical products available sooner and to reduce the costs of developing safe and effective medical products (*FDA Strategy Plan*: <http://www.fda.gov/oc/mcclellan/>). The FDA intends to decrease any avoidable product development costs and increase the quality of drug applications through early meetings with sponsors. Specifically, such efficiency and informativeness are required to improve the design and use of dose-response and pharmacokinetics-pharmacodynamics studies and data, and to discuss the overall biopharmaceutics and clinical pharmacology development strategy needed to support drug dosing and NDA approval. These meetings are voluntary and the sponsor should initiate the meeting request.

The meetings would occur at the end of phase 2A (EOP-2A). For the purposes of this Concept paper, the following definition is used: EOP-2A occurs following the completion of phase 1 and the first set of exposure-response studies in patients, and before beginning phase 2B and phase 3 clinical studies.

Topics for the Meetings

The overall purpose of these meetings is to discuss the exposure-response information during early drug development with the objectives of improving the efficiency of drug development. The exposure-response data would be pertinent to both favorable and adverse effects. In addition, the meetings would discuss critical data on drug interactions, studies in special populations and other PK or PK/PD relationships.

Examples of topics and issues that would shape the agenda for these meetings are:

1. Use of preclinical and early clinical exposure-response information to guide future dose-response, pharmacokinetics-pharmacodynamics (PK-PD) and clinical efficacy studies.
2. Alternatives for design of dose-response and/or PK-PD studies, including the application of mechanistic drug and disease models and simulation, and consideration of related statistical issues.
3. Sampling strategies and study design features of population PK (PD) studies.
4. The type and number of clinical pharmacology studies (PK, PD, and exposure-response) needed to support labeling and approval, e.g., in the areas of drug-drug interactions, food-effect bioavailability and special populations (e.g., elderly, renal impaired patients, poor metabolizers).
5. Designs for studies of special interest, such as exposure-QT, pediatrics PK, and pharmacogenetics studies.
6. Formulation changes, including the considerations pertinent to the need to conduct a bioequivalence study
7. The use of modeling and simulation with exposure-response data to design future clinical trials.

III. Two-Year Pilot Program

During the first 2 years pilot program, CDER will accept an average of 2 meeting requests per month in total from all sponsors. The drugs selection will be chosen based on the criteria under the following three categories.

(1) The Drug

- New molecule entities (NME) that are first in the class or drugs that have been designated as Fast Track products or Continuous Marketing Applications
- Drugs with well-understood mechanisms of action and good exposure response (E/R) relationships

(2) The Data and Methods of Analysis

- Completed clinical studies that can be used as a basis for formulating dose selection strategy

- Example: a titration study that shows an effect and can be analyzed to suggest dose range for later studies
- Available exposure-response information for a reasonable endpoint
 - Example: good dose response data on safety and efficacy with PK/PD analysis
- Good quality and extensive data analysis
 - Example: Quantitative modeling and simulation and disease progression modeling

(3) The Sponsor's Questions

- Questions related to dose selection for phase 2/3 trials, especially if planning to conduct further dose response studies
- Questions related to the analysis of dose-response and/or PK/PD data or modeling/simulation exercises for making development decisions
- Questions related to design and use of population PK/PD or E/R studies for dosing adjustments in special populations
- Questions specific to clinical pharmacology, e.g., which drug interaction studies to conduct
- Questions specific to new target populations, e.g., pediatric bridging studies from adult data
- Questions related to novel development strategies (e.g., genomics) are being proposed
- Questions related to overall optimal clinical pharmacology development plan decisions

IV. Procedure for Requesting the Meetings

A sponsor who is interested in an EOP-2A meeting with CDER should follow the general procedure outlined in the Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products published in February 2000. The type of meetings (EOP-2A) discussed in this Concept paper should be classified as a Type B meeting. The general procedure for requesting and conducting the meetings is depicted in Figure 1.

Prior to submitting a written request for a meeting, the sponsor should contact the immediate office of Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and Office of New Drugs (OND) review division to determine, in principal, the suitable issues and the necessary data to be discussed in the proposed meeting. Once OCPB/OND agree with the sponsor on the overall objectives and contents of the potential meeting, the sponsor should then submit a formal written request (i.e., letter or fax) to FDA (to the attention of OND project managers).

The meeting request should include adequate information for OCPB and OND to determine the utility of the meeting and to identify review staff necessary to discuss the proposed agenda items. The meeting request should include the following information:

1. Product names and application number (if available)
2. Chemical name and structure
3. Proposed indication
4. Dosage form, route of administration, and dosing regimen.
5. A brief statement of the purpose of the meeting. This may include the background information that lead to the request of the meeting.
6. A list of specific issues and expected outcomes from the meeting.
7. A preliminary proposed agenda, including estimated amounts of time needed for each agenda item and designated speaker(s).
8. A list of all individuals (including titles) who will attend the proposed meeting from the sponsor's organization and consultants.
9. A list of FDA staff (not limited to OCPB) requested by the sponsor to participate in the proposed meeting. If a sponsor is not sure which FDA officials should attend the meeting, the applicant does not need to include specific individuals in the request, but should include requested disciplines, if known.
10. The approximate date on which supporting documentation (i.e., the information package described in section IV) will be sent to the FDA.
11. Suggested dates and times (i.e., morning or afternoon) for the meeting.

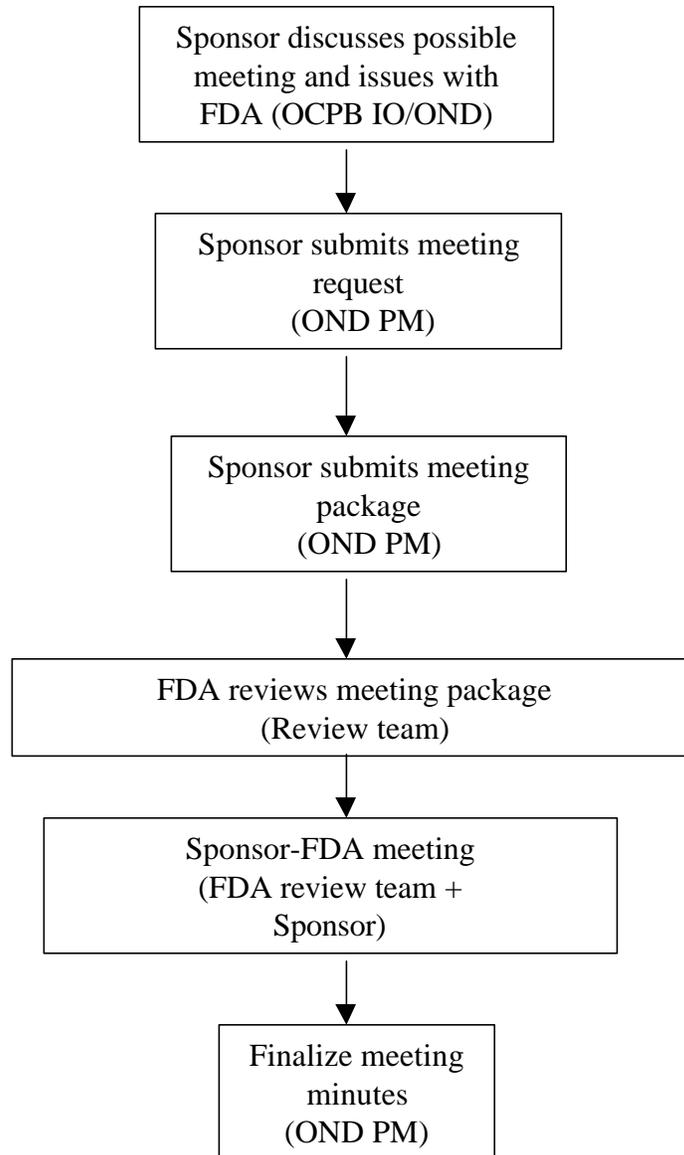


Figure 1. Procedure for requesting and conducting an EOP-2A meeting between a sponsor and FDA. The meeting will be co-chaired by the Directors of OCPB and OND review division, or their delegates. The FDA review team will consist of reviewers from OCPB, OND and other disciplines (e.g, biostatistics, pharmacology/toxicology, chemistry, etc) as required per case basis. OCPB IO: Office of Clinical Pharmacology and Biopharmaceutics Immediate Office, OND PM: Office of New Drug Project Manager.

The Director of OND review Division will determine, in consultation with OCPB Office Director, whether to hold the meeting. FDA should formally respond to the sponsor or applicant within 14 days of receipt of the meeting request. If FDA agrees to the meeting, the written response (i.e., letter or fax) should include the date, time, length, and place of the meeting as well as the expected FDA participants.

If a meeting request is denied, the notification to the sponsor or applicant should include a clear explanation of the reason(s) for the denial (e.g., the criteria for the meeting request are incomplete, or the monthly quota for EOP2A meetings has been met). FDA will consider a subsequent request to schedule the meeting to be a new request.

If a meeting is scheduled by FDA and is later canceled or postponed by the sponsor, the Agency will consider a subsequent request to schedule the meeting to be a new request (i.e., a request that merits a new set of time frames described above). FDA will take reasonable steps to avoid the cancellation or postponement of a scheduled meeting. However, when a meeting is postponed by FDA, the Agency should generally reschedule the meeting to take place within 30 days of the date of the originally scheduled meeting.

V. Information Package

To facilitate the discussions in the meeting, the sponsor should organize an information package according to the proposed agenda. The package should be submitted to FDA (to the attention of OND project managers) at least 4 weeks prior to the scheduled meeting. The cover letter accompanying the information package should clearly identify the date, time, and subject of the meeting. Although the contents of the information package will vary depending on the product, indication, phase of drug development, and specific issues to be discussed, information packages generally should include the following:

1. Product names and application number (if available)
2. Chemical name and structure
3. Proposed indication
4. Dosage form, route of administration, and dosing regimen.
5. A brief statement of the purpose of the meeting. This may include the background information that lead to the request of the meeting.
6. A list of specific issues and expected outcomes from the meeting.
7. Summary tables of available exposure-response studies, which describe the study designs.
8. Summaries of relevant exposure-response data in table and figure formats.
9. Proposed study designs or analysis methods if they are to be discussed.
10. Preliminary analysis (if available) and its interpretation that support the proposed designs or analysis methods.

VI. Procedure for Conducting the Meetings

The OCPB/OND co-chairs or facilitator for a meeting should provide initial structure to the meeting by making introductions and stating the objectives and goals of the meeting. To ensure the accuracy of documentation, all representatives of the sponsor should provide business cards or provide the necessary information on a sign-in sheet. The chair

or facilitator should identify the individual who will record the minutes and keep time, if appropriate.

At the end of the meeting, the chair or facilitator should summarize all important discussion points, decisions, recommendations, agreements, disagreements, and action items for the benefit of all meeting attendees. Attendees should be provided the opportunity to comment. If there are any differences of opinion regarding the outcome of the discussion, the chair or facilitator should ensure that the issues are resolved to the extent practicable. The FDA recorder (e.g. OND project manager) should document this summary as the official minutes.

VII. Documentation

Meeting minutes will be prepared by the OND project manager. The meeting minutes should summarize in bulleted form the important discussion points, decisions, recommendations, agreements, disagreements, issues for further discussion, and action items. The official minutes should be issued to all FDA attendees (with copies to appropriate files) and to the sponsor within 30 days of the formal meeting.

Sponsors may provide the assigned OND project manager with a draft of the firm's minutes in writing, or may identify at the end of the meeting the critical outcomes they believe should be included in the meeting documentation. Draft minutes provided by the sponsor are useful only if submitted promptly. The official minutes are prepared by OND project manager. FDA will not generally comment on draft minutes submitted to the Agency by a sponsor, but may do so where they reflect major differences in view as to the outcomes of the meeting. A sponsor or applicant who identifies major differences in view as to the outcomes of a meeting should communicate these issues with the Agency. Major differences will ordinarily indicate a need for further discussion.