Guidance for Industry

End-of-Phase 2A Meetings

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

September 2009
Procedural

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Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides information on end-of-phase 2A (EOP2A) meetings for sponsors of investigational new drug applications (INDs). The purpose of an EOP2A meeting is to facilitate interaction between FDA and sponsors who seek guidance related to clinical trial design employing clinical trial simulation and quantitative modeling of prior knowledge (e.g., drug, placebo group responses, disease), designing trials for better dose response estimation and dose selection, and other related issues. This guidance is intended to further FDA initiatives directed at identifying opportunities to facilitate the development of innovative medical products and improve the quality of drug applications through early meetings with sponsors.

An EOP2A meeting would occur after the completion of clinical trials that provide data on the relationship of dosing and response for the particular intended use (including trials on the impact of dose ranging on safety, biomarkers, and proof of concept). For the purposes of this guidance, *end of phase 2A* occurs after the completion of phase 1 trials and the first set of exposure-response trials in patients, and before beginning phase 2B (i.e., patient dose-ranging trial) and phase 3 clinical efficacy-safety trials. In the context of drug development programs, discussions at an EOP2A meeting could include exploration of dose estimation and dose selection to use in late stage efficacy trials. Where novel trial designs are a possibility, their utility and applicability could be discussed at an EOP2A meeting.

This guidance focuses on the following specific topics:

- Objectives of the EOP2A meeting
- Considerations for evaluating EOP2A meeting requests
- Useful information for an EOP2A meeting package
- EOP2A meeting arrangements

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

This document does not discuss the general procedures for requesting, scheduling, conducting, and documenting formal meetings. For general information on those topics, see the guidance for industry on *Formal Meetings with Sponsors and Applicants for PDUFA Products* (the Formal Meetings guidance).[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The FDA has a long-standing interest in defining dose-response relationships and pharmacokinetic/pharmacodynamic (PK/PD) relationships (i.e., exposure-response) for the desired (effectiveness) and undesired (toxicity) effects of new drugs.[3] Accurate dose-response information is important for understanding how patients should take drugs to maximize desirable effects and minimize undesirable effects. Dose selection for phase 2 and phase 3 trials is a challenge in many drug development programs, and poor choice may lead to trial failure. Improving early dose selection may increase the likelihood of future trial success.

FDA recognizes trial planning may be improved by clinical trial simulations that employ quantitative models of drug exposure-response, effects in placebo group, and disease progression. FDA would like to encourage the best use of this science to facilitate the exploration of trial design alternatives to increase the likelihood for successful trials.

A. Strategies for Early Dose Selection

Currently, FDA and sponsors participate in meetings where drug development strategies are discussed, such as pre-IND, end-of-phase 2, pre-NDA or pre-BLA, and general guidance meetings. Often, these meetings do not allow for the in-depth discussion of modeling and simulation tools and approaches that could be helpful in dose estimation and selection. Our experience suggests that it may be important for sponsors and FDA to discuss the use of quantitative drug development methods (e.g., trial simulation using disease, drug, placebo, and dropout models) before conducting phase 2B and phase 3 clinical trials.

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[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] For guidance related to exposure-response trials, see the guidances for industry on *Exposure-Response Relationships — Study Design, Data Analysis and Regulatory Applications*; *Dose-Response Information to Support Drug Registration (International Conference on Harmonisation (ICH) E4)*; and *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

An EOP2A meeting does not replace other meetings, but rather provides an additional opportunity for in-depth, exploratory discussion with FDA focused on optimizing next steps in drug development. The goal of earlier discussions is to avoid pitfalls in dose selection and clinical trial design that could result in subsequent safety issues due to selecting doses that are too high, in efficacy issues due to selecting doses that are too low, or in unnecessary clinical trial failure from not accounting for disease natural history, inappropriate patient selection, effects in the placebo group, or dropouts. The Agency specifically encourages sponsors to use all prior knowledge (including data and analyses, quantification of disease variability, subgroup heterogeneity, and dose (concentration)-response models in the development of clinical trial simulations) to make more informed drug development decisions on trial design and dosage regimen selection.

B. EOP2A Pilot Program

Under a pilot program started in 2004, FDA conducted a series of EOP2A meetings where data were modeled to simulate next trial design options. The main focus for the pilot was the use of the simulation results to inform the design parameters of subsequent trial and dosage regimen choice(s). Other topics included balancing efficacy and toxicity in terms of dose response, genotype, drug-drug interactions, and drug formulation.

Modeling and simulation efforts utilized information from prior clinical trials, such as dose response, disease change over the likely duration of the trial, effects in the placebo group including time-course, and patient baseline data. Typical sources of information included literature, previous trials within the organization, and publicly available databases. Clinical trial simulations were conducted to evaluate the adequacy of the proposed trial design and alternatives with respect to the predicted probability that the trial would successfully discriminate the treated groups from the control groups (e.g., placebo). Therapeutic areas in the pilot program included HIV infection, prostate cancer, bacterial infection, seizure disorders, pain, and obesity. Post-meeting utility evaluations indicated that sponsors found EOP2A meetings valuable.[4]

FDA often performed the modeling analyses for the pilot program. However, in the future we expect that sponsors will perform these modeling analyses and include them in the meeting package so that FDA can review this information in planning subsequent work. In addition, FDA may perform in-house modeling to address particular problems or to independently assess the sponsor's model. It is expected that FDA pharmacometrics, biostatistics, and medical reviewers will generally perform most of the review work for these meetings. Reviewers from other review disciplines will participate, as needed, in the preparation and conduct of these meetings, and FDA intends to provide consolidated FDA comments to the sponsor.

[4] See Wang, Y., V.A. Bhattaram, P.R. Jadhav, L.J. Lesko, R. Madabushi, J.R. Powell, W. Qiu, H.Sun, D.S. Yim, J.J. Zheng, J.V.S. Gobburu, "Leveraging Prior Quantitative Knowledge to Guide Drug Development Decisions and Regulatory Science Recommendations: Impact of FDA Pharmacometrics During 2004-2006," *Journal of Clinical Pharmacology,* 48(2):146-156, 2008.

III. THE EOP2A MEETING

The overall purpose of an EOP2A meeting is to discuss options for trial designs, modeling strategies, and clinical trial simulation scenarios to improve the quantification of the exposure-response information from early drug development. The goal of these meetings is to optimize dose selection for subsequent trials to improve the efficiency of drug development. The exposure-response data discussed might be pertinent to evaluation of efficacy outcomes or adverse outcomes. In addition, the meetings would provide opportunities for discussions of complex issues pertaining to drug interactions, trials in special populations defined by genetic characteristics or other biomarkers, and other PK or PK/PD relationships.

A. Objectives of an EOP2A Meeting

The main objectives of an EOP2A meeting are to help select the dosing regimens for the next phase (typically phases 2 and 3) of drug development and to design informative dose-response trials that will inform later phase clinical trials by best incorporating prior quantitative knowledge.

Preferably, industry and FDA scientific staff will agree on the modeling and simulation approaches before the EOP2A meeting so the meeting time can be used to interpret the results and discuss dose and/or trial design issues. The sponsor might also seek the advice of FDA on other issues, such as the design of exploratory trials that employ adaptive trial designs intended to be flexible in the choice of one or more doses for further evaluation and patient selection criteria.

Topics for discussion at an EOP2A meeting might include:

- Use of quantitative information for dose selection using mechanistic or empirical relationships among biomarker, surrogate endpoints or clinical endpoints for both effectiveness and safety

- Use of quantitative knowledge of drug effects in animals and human subjects to aid in both dose-ranging trial design and safety assessment. Examples include:
  - Effects in the placebo group
  - Disease severity (baseline) effect
  - Disease endpoint variability and time course

- Use of available preclinical and clinical exposure-response data and discussion of implications for dose-response trial design

- Contrasting alternative trial design strategies (e.g., parallel, cross-over, adaptive, randomized withdrawal) and analyses (e.g., Bayesian)

- Use of pharmacogenetic information from preclinical studies and clinical trials and discussion of the implications of genetic factors on PK, PD, or both. The discussion

might include a quantitative evaluation of genetic effects on dose selection and the use of genetics to inform assessments of drug safety and effectiveness in future trials.

- Discussion of blood or DNA sampling strategies and other trial design features to optimize the usefulness of future trials

- Discussion of the utility of PK/PD data for dosing adjustments in special populations (e.g., pediatrics)

B. EOP2A Meeting Requests

The general procedure for requesting an EOP2A meeting should be that described in the Formal Meetings guidance. The EOP2A meeting is considered a Type C meeting. The sponsor's written request (i.e., letter or fax), which should be directed to the appropriate Division Director within the Office of New Drugs (OND), should (1) specifically state that the request is for an EOP2A meeting and (2) ask that the request be forwarded immediately to the Director of Pharmacometrics in the Office of Clinical Pharmacology (OCP) and the Director of the Office of Biostatistics (OB). All three directors will consult and determine whether to hold the meeting.

Sponsors are encouraged to submit all relevant information with the meeting request, including data, any models or simulations of trial design, or disease or outcome models that have been explored that provide insight into the issues for discussion. Sponsors can elect to submit the electronic data and model files only if the meeting is granted. If the sponsor requests that the FDA develop model(s) for the submitted data, the sponsor should request a meeting date at least 10 weeks after FDA's receipt of the meeting package. While FDA modeling is feasible, FDA resources are limited; therefore, decisions to do this work, including timelines, are made on a case-by-case basis. The following information should be included in the meeting request:

- A list of objectives, specific issues for discussion, and expected meeting outcomes.

- A list of all individuals (with titles) from the sponsor's organization and consultants who will attend the proposed meeting. Sponsors should provide names of scientific experts (and the preferred channel of communication) who can provide clarification on the data sets and/or the quantitative analyses to facilitate communication between FDA scientific staff and the sponsor's counterparts, especially when analyses are to be conducted in the limited time between the EOP2A meeting request and the meeting date.
- A list of completed trials describing key design features.

- Summary reports of the modeling and simulation to support the proposed trial design and dose range selection.

- Questions about drug development issues, including trial duration, dose individualization, pharmacogenomics, and data analyses.

- Proposed trial designs or analysis methods if they are to be discussed.

- Current Investigator's Brochure and relevant literature and/or public information.

Considerations used by FDA to evaluate a meeting request might include:

- Are the appropriate FDA resources available for the project?
- Has the sponsor conducted necessary modeling and simulation to support the discussion of questions related to the development of the drug?
- Would the product fill an unmet therapeutic need?
- Does past experience suggest that there could be a high clinical trial failure rate in the therapeutic area?
- Does FDA have unique experience that would be of particular value to the project?
- Would the project benefit from modeling and simulation?

To date, most requests for EOP2A meetings have been granted. On some occasions, the request did not fit the intended purpose of the meeting or there were insufficient resources to conduct the meeting in a timely manner and a meeting was not granted.

C. Useful Information for an EOP 2A Meeting Package

General instructions regarding timing and contents of the information package are found in the Formal Meetings guidance.

Examples of useful background information specific to the EOP2A meeting package include:

- Electronic data sets and modeling files.
- Detailed modeling and simulation reports and interpretation that support the proposed designs or analysis methods, including relevant tables and figures.
- Appropriate nonclinical and phase 1 data and any modeling performed pertaining to pharmacokinetic variability due to intrinsic and extrinsic factors.

Data sets should be submitted as SAS transport files with model codes and final model output submitted as ASCII files with 'txt' extension. FDA accepts results of pharmacometric analyses conducted using a variety of software. Sponsors should use their scientific judgment in selecting appropriate software.

D. EOP2A Meeting Arrangements

The procedures for conducting the meeting are described in the Formal Meetings guidance. The meeting topics determine which FDA office(s) will chair the meeting (e.g., OND, OB, OCP). The final minutes and recommendations will be issued through the OND division.

Once the decision has been made to have the meeting, the appropriate FDA staff and sponsor staff can communicate, usually by telephone, to agree on the following:

- meeting objectives and attendees
- information that will be supplied for the meeting
- model and data submission formats
- modeling approaches and additional simulation conditions, if appropriate
- collaboration on additional modeling and simulation work to shorten the wait time before the meeting, as appropriate
- the meeting date (usually 6 to 10 weeks after FDA's receipt of the meeting package, data, and models)
- whether the meeting will be in person or by telephone

FDA recognizes time is important if these meetings are to have value during drug development. The date set for the meeting will depend upon other priorities and the need for FDA staff to perform additional modeling and simulation work. Should the meeting be granted, FDA will make every effort to hold the meeting in a timely manner.

The exploratory nature of the analyses and discussions at an EOP2A meeting are intended to result in suggestions and options to assist the sponsor in optimizing the next steps of drug development. Clinical trial simulations and modeling should be shared between the sponsor and FDA staff before the meeting so that the actual meeting focuses on the interpretation and recommendations for next steps. In addition to the meeting minutes, any additional FDA-conducted modeling and simulation materials derived from sponsor-provided data will be given to the sponsor following the meeting. Any further follow-up can be decided at the meeting.