Guidance for Industry
End-of-Phase 2A Meetings

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DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Robert Powell at 301-796-1589.

U.S. Department of Health and Human Services
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September 2008
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TABLE OF CONTENTS

Guidance for Industry [1]

End-of-Phase 2A Meetings

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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, disease, placebo), designing trials for better dose response estimation and dose selection, and other appropriate 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 studies that provide data on the relationship of dosing and response for the particular intended use (including studies 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 studies and the first set of exposure-response studies in patients, and before beginning phase 2B (i.e., patient dose-ranging trial) and phase 3 clinical efficacy-safety studies. 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

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 and undesired 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 studies is a challenge in many drug development programs and 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 dose-response, placebo effect, 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 strategy is 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 quantification and analytical 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.

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 avoiding 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, placebo effect, 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 computer 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, placebo effects including time-course, and patient baseline data. 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 study 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 pharmacometricians and biostatisticians will generally perform most of the review work for these meetings. Reviewers from other review disciplines will participate in the preparation and conduct of these meetings.

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 during 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 critical data on drug interactions, studies 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 of drug development and to design informative dose-response and dose-selection clinical trials that will inform later phase clinical trials by best incorporating prior quantitative knowledge.

Ideally, industry and FDA scientific staff will have agreed upon 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 studies that employ adaptive trial designs intended to be flexible in the choice of one of 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
- 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:
    - Placebo effect
    - Disease severity (baseline) effect
    - Disease endpoint variability and time course

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