Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Office of Clinical Pharmacology, at 301-796-5008 or OCP@fda.hhs.gov.

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

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance outlines the recommended format and content for a sponsor to submit physiologically based pharmacokinetic (PBPK) analyses to the FDA to support applications including investigational new drug (INDs) applications, new drug applications (NDAs), biologics license applications (BLAs), or abbreviated new drug applications (ANDAs). To enable efficient and consistent review, the FDA recommends including the following five sections in a PBPK study report: (1) Executive Summary; (2) Materials and Methods; (3) Results; (4) Discussion; and (5) Appendices. The content of each section is described in detail below. This guidance does not address methodological considerations and best practices for the conduct of PBPK modeling and simulation, or the appropriateness of PBPK analyses for a particular drug or a drug product (i.e., both small molecules and biologics). The decision to accept results from PBPK analyses in lieu of clinical pharmacokinetic (PK) data is made on a case-by-case basis, taking into account the intended use for the analyses, as well as the quality, relevance, and reliability of the study results.

In general, FDA's guidance documents 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

[1] This guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

A PBPK analysis uses models and simulations that combine physiology, population, and drug characteristics to mechanistically describe the PK and/or pharmacodynamic (PD) behaviors of a drug (Rowland, Peck, et al. 2011; Rostami-Hodjegan 2012). Throughout a drug's life cycle, PBPK model predictions can be used to support decisions on whether, when, and how to conduct certain clinical pharmacology studies, and to support dosing recommendations in product labeling (Zhao, Zhang, et al. 2011; Jones, Chen, et al. 2015; Shepard, Scott, et al. 2015; Wagner, Zhao, et al. 2015). Because of the lack of regulatory guidance, the format and content of PBPK analyses that are submitted to the FDA vary significantly across drug developers. Therefore, standardizing the content and format of PBPK study reports that are submitted to the FDA can facilitate FDA's efficient assessment, consistent application, and timely decision making during regulatory review and is the goal of this guidance.

III. FORMAT AND CONTENT

PBPK analyses may be appropriate at multiple points in the drug development process, for example in IND applications, NDAs, BLAs, ANDAs, or in the postmarketing stage. The depth and breadth of PBPK analyses at each stage may vary significantly because of the availability or quality of clinical data. The FDA, however, suggests including the following sections in the PBPK study report for all PBPK analyses.

A. Executive Summary

The executive summary should include the rationale for conducting the PBPK analyses, provide a succinct overview of model development and simulation scenarios, and summarize the key conclusions of the report. This section should clearly convey how the analyses address a specific scientific question in a clinical setting in support of a regulatory decision.

B. Introduction

The section should provide (1) a high-level synopsis of the drug's PK and PD properties; (2) the exposure-response relationships for the efficacy and safety of the drug; and (3) a brief regulatory history to provide context for the PBPK analyses.

C. Materials and Methods

This section should include sufficient information to allow the FDA reviewers to evaluate the submitted modeling and simulation results and to conduct supplemental analyses when necessary. Sharing this information streamlines the review process, and enables further analyses (Zhao, Rowland, et al. 2012). Suggested components of the materials and methods section include the following:

1. Overview of Modeling Strategy

This section should detail the modeling procedures, including the model development, model verification/modification, and model application. The procedures should be outlined in a step-wise manner using a workflow, decision-tree, table, or other representation. The sponsor should appropriately reference the data and studies used in each step of the modeling process.

2. Modeling Parameters

All system and drug-specific components, as well as the sources of parameter values, should be clearly specified. If a parameter value has been estimated, the data source and estimation method should be described. When clinical PK data are used to optimize model parameters, justification for selecting a particular optimization technique should be documented. All model assumptions, including the biological and/or pharmacological rationale for the assumptions, should be clearly stated (Zhao, Rowland, et al. 2012).[2] The sponsor should present the modeling parameters using a table or other visual representation.

3. Simulation Design

The description of simulation conditions should include the following information for the model development, verification, and application:

- Route, dose, formulation of the drug product, time of administration, and fasting or fed conditions
- Simulation duration
- Demographics of the virtual population
- Number of simulation studies for a specific scenario (simulation trials)
- Number of virtual subjects in each simulation trial

4. Electronic Files and Other Documentation

Submitting electronic files streamlines the review process and allows for effective communication between the FDA and the sponsor or the applicant. Electronic files related to modeling software and simulations should be submitted along with the study report. Supporting information such as clinical pharmacokinetic or pharmacokintetic/pharmacodynamic data used in PBPK analyses or a scientific publication or an orientation document for submitted simulation data and model files can also be included. Cross-references to other parts of the report and other parts of the application should be provided with hyperlinks. If necessary, consult the FDA regarding the feasibility of submitting certain types of electronic files.

[2] International Programme on Chemical Safety,"Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment" available at http://www.who.int/ipcs/methods/harmonization/areas/pbpk_models.pdf.

5. Software

The FDA does not require the use of a particular PBPK modeling software. Because of substantive differences in software models and versions, sponsors should include information on the PBPK modeling software. Table 1 below highlights the information that should be included regarding commercial PBPK modeling software (commercial PBPK platform) versus custom modeling software (e.g., commercial software that has been modified with custom codes or otherwise revised for the purpose of PBPK modeling).

Table 1. Software Information for PBPK Modeling

Suggested Software Information	PBPK Models	
	Custom Modeling Software	Commercial PBPK Platform
Name and version of the software	Yes	Yes
Schematic view of model structure and differential equations based on established theoretical or biological basis	Yes	Optional
Parameterization of system information and sources of parameter values	Yes	Optional
Table of drug-dependent parameters for the investigational drug of interest, including names, values, units, and sources of the parameters, prediction algorithms, and assumptions being made	Yes	Yes
Literature references and the sponsor's prior experience/knowledge in using the software for PBPK modeling (to help the reviewer understand how PBPK models are coded using the modeling software that was tested)	Yes	Yes
Manuals on model implementation of the software (to be provided as supporting documents)	Yes	Optional
Library system models (e.g., virtual population), including justifications for any modifications made to the model's physiological parameters by the sponsor	Not applicable	Yes
Library drug models, including justifications for any modifications to the model made by the sponsor and information on model verification	Not applicable	Yes

D. Results

The sponsor should both demonstrate that the PBPK model is relevant and appropriate for subsequent analyses and describe the results of model application. Details on suggested components of model verification and model application are provided below.

1. Model Verification and Modification

The sponsor should clearly present the methodological approach used to verify the model, confirm model results, and conduct sensitivity analyses to allow the FDA to evaluate the robustness of the model. The methods best suited for model verification are dependent upon the availability of clinical data to independently either confirm or reject the proposed model. Clinical PK data (e.g., steady-state plasma PK data or certain drug-drug interaction data) are

generally expected to establish confidence in the appropriateness of the PBPK model in addressing the study question (Vieira, Kim, et al. 2014, Wagner, Pan, et al. 2015, Wagner, Pan, et al. 2016).

Sensitivity analyses are important components of model verification, especially for uncertain parameters with a high potential to influence the outcome of the simulation. For example, if a PBPK model is used to predict the inhibition effect of an investigational drug on the exposure of a cytochrome P450 substrate, sensitivity analyses—such as simulations that test a plausible range of inhibition potency (e.g., a reversible inhibition constant K_i)—would be informative. Results of sensitivity analyses for uncertain parameters should be discussed in the context of the simulation conditions and potential clinical consequences.

In some instances, model parameters can be refined during model verification. Such modifications are important aspects of model refinement and should be described. If the assumption of the model parameters cannot be confirmed during modification, further verification may be needed before the model can be applied to predict untested clinical situations. The ultimate goal of PBPK analyses is to obtain the most accurate model that can predict unknown situations with confidence. The sponsor should clearly demonstrate that the proposed PBPK model is relevant to the study population and to the modeling purpose/question asked, appropriate for the drug under investigation, and robust enough to handle perturbations in uncertain study parameters.

2. Model Application

The sponsor should present the results of using the verified PBPK model to address the study question using tables, graphs, and text where appropriate. The best data representation is dependent upon the study question, PBPK model, and other relevant parameters.

E. Discussion

In this section, the sponsor should discuss how the PBPK modeling and simulation analyses adequately address the proposed scientific, regulatory, or clinical questions. The basis for any requests to waive the conduct of clinical studies should be discussed and well substantiated. If simulations are used to support specific dosing recommendations to be tested in future clinical trials or to be included in prescription product labeling, the proposed dosing recommendations should be discussed within the context of known exposure-response relationships and the level of confidence in the PBPK model for the intended application (Wagner, Zhao, et al. 2015). The sponsor should also note the limitations of its modeling approach and assess the potential impact of these limitations on the study results and interpretation.

F. Appendices

The following information should be included in the appendices.

1. List of Tables

Provide a list of all tables used throughout the document.

2. List of Figures

Provide a list of all figures used throughout the document.

3. Table of Acronyms and Abbreviations

Spell out all acronyms and abbreviations used in the document.

4. References

Include a list of all references.

IV. REFERENCES

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