Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

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

August 2018
Clinical Pharmacology

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Contains Nonbinding Recommendations

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry[1]

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance outlines the recommended format and content for a sponsor or applicant to submit physiologically based pharmacokinetic (PBPK) analyses to the FDA to support applications including, but not limited to, investigational new drug applications (INDs), 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 six sections in a PBPK study report: (A) Executive Summary; (B) Introduction; (C) Materials and Methods; (D) Results; (E) Discussion; and (F) 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. The decision to accept results from PBPK analyses in lieu of clinical pharmacokinetic (PK) data is made on a case-by-case basis, considering the intended uses, as well as the quality, relevance, and reliability of the results from the PBPK analyses.

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

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. Throughout a drug's life cycle, PBPK model predictions can be used to support decisions

[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.

on whether, when, and how to conduct certain clinical pharmacology studies, and to support dosing recommendations in product labeling. Because of the lack of regulatory guidance, the format and content of PBPK analysis reports that are submitted to the FDA vary significantly. The goal of this guidance is to standardize the content and format of these reports to facilitate the FDA's efficient assessment, consistent application, and timely decision making during regulatory review.

III. FORMAT AND CONTENT

The FDA suggests including the following sections in the PBPK study report for all PBPK analyses.

A. Executive Summary

The executive summary should include the objectives and 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

This section should provide the following components, if available: (1) a high-level synopsis of the drug's physicochemical, PK, and PD properties; (2) the exposure-response relationships for the efficacy and safety of the drug to the extent that they are known; (3) a brief PBPK-related regulatory history (i.e., prior interactions with the FDA and other regulatory agencies) to provide context for the PBPK analyses; (4) cross-referencing to PBPK study reports previously submitted to the FDA for different intended uses at different stages of the development of the same drug substance or the same drug product.

C. Materials and Methods

This section should include sufficient information to allow FDA reviewers to duplicate and evaluate the submitted modeling and simulation results and to conduct supplemental analyses when necessary. Suggested components of the materials and methods section include the following:

1. Overview of Modeling Strategy

This section should detail the modeling procedures, including 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-specific and drug-specific components, as well as the sources of parameter values, should be clearly specified and justified (e.g., appropriate references). If there are several sources of one parameter, the selection should be described. If a parameter value has been estimated, the data source and estimation method should be described or appropriately referenced. The use of clinical PK data to optimize model parameters should be described and justified. Key model assumptions that may impact the model application, including biological and/or pharmacological rationales, patient/disease-related assumptions, or mathematical representations of the biological system, should be clearly stated. The sponsor should present the modeling parameters using a table or other visual representation. For example, drug-dependent parameters for the investigational drug of interest, including names, values, units, and sources of the parameters, prediction algorithms, and assumptions should be summarized in table format. Procedures for assessing uncertainty (e.g., using sensitivity analysis) of the PBPK model parameters should be provided.

When library drug and system models (e.g., a virtual population) within a specific software platform are used, the sponsor should justify the use of these models and clearly identify and justify modifications made to the library models.

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 (either substrate or modulator), time of administration, and fasting or fed conditions
- Dosing regimen of the drug product
- Duration of the simulated trials
- Demographics of the virtual population and distribution of demographic information
- Number of simulation studies for a specific scenario (simulated trials)
- Number of virtual subjects in each simulated trial
- Settings for differential equation integrators, when applicable

4. Electronic Files and Other Documentation

Submitting electronic files streamlines the review process and allows for effective communication between the FDA and the sponsor. Examples of permissible file types can be

found in the *Specifications for File Format Types Using eCTD Specifications* document.[2] This includes permissible file types/extensions and the modules in which they are permissible. In addition, the *Technical Rejection Criteria for Study Data* document denotes what modules' study data validation rules will not be applicable.[3]

Electronic files related to modeling software and simulations should be submitted along with the PBPK study report. Supporting information such as clinical PK or PK/PD data used in PBPK analyses, 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 or locations of the modules of an IND, NDA, BLA, or ANDA submission, if applicable. If necessary, consult the FDA regarding the feasibility of submitting certain types of electronic files.

5. Software

The FDA does not recommend the use of any particular software for PBPK modeling. As PBPK models are highly complex in nature, sponsors anticipating the application of PBPK modeling in their drug development program should communicate early with the FDA. Additional technical and instructional information beyond the minimum data listed below may be needed to ensure that the FDA has sufficient working knowledge of the specific PBPK model and software to facilitate a timely review.

The following information should be included in the submission to facilitate a timely review:

- Name and version of the software[4]
- Schematic view of the model structure and mathematical equations (or relevant references) based on established theoretical or biological knowledge
- Parameterization of system information and sources of parameter values, such as databases used to describe the population variability and correlation between parameters
- User's manual (i.e., instructions on how to run the code)

[2] The Specifications for File Format Types Using eCTD Specifications can be found at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm347471.pdf

[3] The Technical Rejection Criteria for Study Data can be found at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

[4] The sponsor should provide sufficient documentation regarding any changes made by the software vendor to the version of the software over the period of PBPK model development and describe how these changes may impact the performance of the submitted model.

D. Results

The sponsor should both demonstrate that the PBPK model is appropriate for the intended uses and describe the results of model application. Descriptive statistics or other appropriate analysis on the results of model-generated simulations should be presented, and when applicable, compared to observed data. In addition, a summary of supplementary materials should be included. Often, supplementary tables and figures are needed to facilitate the assessment of a PBPK analysis. Details on suggested components of model verification and model application are provided below.

1. Model Verification and Modification

This section of the report should provide sufficient information to clearly demonstrate that the proposed PBPK model is appropriate for the modeling purpose or question asked for the particular drug product and study population and is robust enough to respond to perturbations in uncertain parameters. To allow the FDA to evaluate the robustness of the models, the sponsor should clearly present results from the methods used to verify the model, confirm model results, and conduct sensitivity analyses. The sponsor should include and discuss the procedures used for model verification (both the drug and system models). Results of sensitivity analyses for uncertain parameters should be discussed in the context of the simulation conditions and potential clinical relevance.

In some instances, model parameters may be refined during model verification. Such modifications are important aspects of model refinement and should be described and justified. If the assumptions of the model parameters cannot be confirmed during modification, further verification to predict clinical scenarios that were not previously evaluated should also be submitted.

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.

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 incorporated in prescription drug labeling, the proposed dosing recommendations should be discussed and justified within the totality of evidence, including the context of known exposure-response relationships and the level of confidence in the PBPK model for its intended uses. See the FDA's guidance for industry entitled *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Format and Content* for more details

on specific language to include in the labeling.[5] The sponsor should also note the limitations of its modeling approach in this section of the report and assess the potential impact of these limitations on the PBPK 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.

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.