Provisional Translation (as of February 2021)*

PSEHB/PED Notification No. 1221-1
December 21, 2020

To: Director of Prefectural Department of Health

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models

In recent years, much attention is being given to drug development strategies that use modeling & simulation (M&S) based on mathematical models in an attempt to predict relationships of pharmacokinetics, pharmacological action, and the efficacy or safety following administration of drug products. One of the M&S techniques is an analysis using a physiologically based pharmacokinetic (PBPK) model by incorporating information such as human physiology, and biochemical and physicochemical information of the drug into the model. A PBPK model is a useful technique for investigating drug interactions, predicting pharmacokinetics in special populations (e.g., pediatrics), and determining dosage and regimen.

Taking account of the recent increase in the use of PBPK analyses to support marketing applications, Ministry of Health, Labour and Welfare has prepared "Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models," to enable a sponsor or applicant to report PBPK analyses appropriately. We ask you to inform manufacturers and sellers placed under your administration to utilize this for their business operations.

This guideline provides points to consider and basic principles in preparing analysis reports involving PBPK models in drug development as described in the Introduction. The guideline is based on the current scientific knowledge. When a new finding is obtained through advancement in academic knowledge, science, and technology, please take a flexible approach based on sound scientific decision together with the guideline.

∗ This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

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1. Introduction

1.1. Background and objectives

Physiologically based pharmacokinetic (PBPK) models are mechanistic mathematical models describing physiological, physicochemical, biochemical, and pharmacokinetic factors. These models are described by mechanistic model structures and parameters, consider absorption, distribution, metabolism, and excretion of drugs, etc., and enable dynamic prediction of changes in tissue and blood/plasma concentrations of drugs, etc. To explain the mechanism of pharmacokinetic behaviors of a drug and effects of particular factors thereon, a PBPK model analysis involves modeling and simulation that combine physiology, drug, and population characteristics.

Throughout the entire process of drug development, prediction using a PBPK model has the potential to provide information useful in decision-making concerning the need and methods for the conducting a particular clinical trial. Furthermore, the simulation results of an appropriately conducted PBPK model analysis may be used for adjustment of dosage and administration of a drug, decisions concerning the requirement for alerts, and the setting of rationale for these measures. PBPK model analyses are considered useful, particularly in qualitative/quantitative prediction of drug interactions and the setting rationale for dosage and administration in clinical trials in pediatric subjects. PBPK model analyses may also be used to investigate the initial dose in first-in-human studies.

The objective of this guideline is to ensure the consistency of data submitted to the regulatory authority, to facilitate timely decision-making in clinical trial consultations and regulatory reviews, etc., and to standardize the content of PBPK model analysis reports for the appropriate provision of information.

This guideline summarizes points to consider and basic principles in reporting the results of PBPK model analysis, so that assessment results obtained by using PBPK model analysis in drug development are appropriately reported to the regulatory authority. It should be noted that the usability of the simulation results by a PBPK model analysis is determined specifically for each drug, considering the objective and reliability of the analysis.

Each item described in this document has been discussed based on the current

scientific knowledge. When new knowledge is obtained through future advancement in theoretical and applied research, consideration for flexible responses will be required based on sound scientific decisions.

1.2. Scope

This guideline applies to PBPK model analyses to be submitted to the regulatory authority in applications for approval and clinical trial consultations, etc., throughout the life-cycle of a drug.

2. Content of an analysis report

2.1. Summary

This section should summarize the objective of the conduct of PBPK model analysis, methods (background information used for model building, methods for model buiding and model validation, etc.), results, discussion and important conclusion.

2.2. Objective

This section should describe the objective of PBPK model analysis, including the positioning of the analysis in development phases of the drug product, the background of and reasons for conducting the analysis in a concise manner.

2.3. Background information

This section should summarize information concerning clinical development strategies related to PBPK model analysis of the drug product, positioning of PBPK model analysis in clinical development of the drug product, and the drug product per se. In devising clinical development strategies related to PBPK model analysis, development plans that allow acquisition of data optimal for model validation based on the pre-defined purpose of the analysis should be considered. It is desirable to present the positioning of the analysis and development strategies by using figures and tables, etc., as necessary.

The drug information related to model building should be described by emphasizing pharmacokinetic properties in absorption, distribution, metabolism, and excretion obtained from *in-vivo* and *in-vitro* studies. If possible, mass-balance results quantitatively presenting the fraction of drug absorption, information of first-pass

metabolism and protein binding, and fraction on contribution for individual drug clearance pathways (e.g., drug-metabolizing enzymes, drug transporters, renal excretion) should be provided with references. It is desirable to provide visually comprehensible explanations using graphical representations, when necessary.

Data concerning effects of physicochemical properties of the drug, pharmacokinetic interactions, and pharmacogenetic factors on pharmacokinetics as well as additional information should also be described as necessary. When a PBPK model is used for prediction of a scenario involving potential changes in drug exposure, background information should also include (1) existing findings on the exposure-response relationship related to a drug's efficacy and safety or (2) drug exposure observed in the pivotal study for efficacy and safety. In estimating pharmacokinetics in specific populations (e.g., pediatrics and renal impairments), information of rationales supporting the validity of system specific parameters (e.g., potentials changes in fraction of contributions rate for individual clearance pathways) should also be presented. If available, a summary of results obtained from prior PBPK model analysis conducted in other populations should be described as necessary.

2.4. Methods of analysis

Study data that are used for analysis such as model validation and parameter estimation should be appropriate in consideration of the objective of analysis.

This section should describe sufficient information to allow regulators to understand and reproduce the details of the analysis (including assumptions made upon planning of the analysis, physiological and drug information related to modeling, the model structure and modeling process, and information concerning simulation conditions and assessment methods, etc.). Concomitantly, the workflow of the model analysis should also be described, including model building, validation, refinement, and application, etc., of the model. It is desirable to include illustrations schematically representing the workflow of the model analysis. Information about the PBPK platform used is also included in this section.

2.4.1. Assumptions

Assumptions on physiological and drug information as well as the assumptions made in the model building need to be clearly described, because they are important in investigating and understanding uncertainties in the model and analysis results.

The structure of the model should be explained in the analysis report. The scientific

rationales of the model structure used should be presented with assumptions related to the model.

Data supporting the appropriateness of the assumptions should be presented, and detailed information concerning model uncertainties as well as impact of the assumptions on the model, the simulation results by a PBPK model analysis and decisions using the simulation results should also be described.

Except for cases in which the rationales and validity of the assumptions made are fully clarified or confirmation thereof is not feasible, the validity of the assumptions made should be assessed by non-clinical or clinical studies or simulation to be conducted subsequently. The method used to investigate the validity of the assumptions should be described with results obtained.

2.4.2. Information of system specific parameters

System specific parameters and their sources should be described, using tables, etc. References as data sources should be attached as necessary, and the setting rationales for parameter values should be described. When the default parameter values within a commercially available PBPK platform were used, a comprehensible statement that the default parameter values were used for the particular platform should be included. If a system specific parameter has been estimated, the method used for estimation should be described. If the system specific parameters were optimized using study data, the validity of optimization should be demonstrated. The validity of the approach used as well as the resulting optimized model should also be described regarding which step of the model building process involved optimization of the system specific parameters. Prerequisites concerning system specific parameters used (e.g., information of the population assumed) should also be described. For example, if a simulation assuming a population of Japanese subjects was conducted, this should be clearly described with information of parameter values in the Japanese population.

2.4.3. Drug information related to model building

Drug parameters used in the model and their sources should be clearly described using tables, etc. In addition, study reports and references should be attached to provide the source of drug parameters (including physicochemical parameters and *in vitro* data*).* If the parameters were optimized using non clinical and clinical data, the methods for optimization of individual parameters (including data used for optimization), optimization process, and validity of the model should be described.

If any parameter used has multiple sources, the selected parameter value should be validated, and its effects on overall outcome should be discussed using approaches such as sensitivity analysis. Factors potentially influencing estimation of parameters should be clearly described, if any. If a drug parameter value has been estimated, the method and data source used for estimation should also be described. Estimated values for individual parameters should be clearly described using tables, etc., and the credibility of these values should be demonstrated as necessary. In addition, pharmacokineric validity of these values should also be discussed.

In predicting drug interaction, information concerning drug parameters for prospective concomitant drugs (e.g., information of selective substrates [or index drugs], inhibitors, or inducers of drug-metabolizing enzymes, etc., appropriateness of the selection, and others) needs to be presented in a similar manner to the investigational drug.

2.4.4. Simulation

Simulation conditions and validity thereof should include the following information concerning model building, validation, and application of the model:

- Route of administration for the investigational drug and concomitant drugs
- Dosage and administration as well as dosage form
- Dosing conditions (fasting, postprandial, etc.)
- Information of the population and study conditions required for simulation (e.g., subject background)
- Number of subjects and trials assumed for each simulation

2.4.5. Methods for model qualification

Methods and approaches used for model validation and sensitivity analyses should be clearly presented.

The model and the simulation results should be evaluated according to the purpose. The evaluation criteria may vary depending on the purpose of analysis. Since model validation should focus on the parts of model building and simulation that are important for the intended purpose, it is important to describe clearly the validation methods used. Model validation should be conducted by comparison of the predicted and observed data, according to the purpose. During this process, comparison from various viewpoints related to the purpose (e.g., dose-dependence [linearity/non-linearity], drug interaction, various routes of administration [e.g., comparison of intravenous and oral administrations], the drug product, etc.) might yield additional

evidence supporting the model validity.

Sensitivity analyses should be conducted specifically for parameters that are likely to influence the simulation results and discussion thereof and that are highly uncertain. All sensitivity analyses conducted should be clearly described in the report. The validity of the range of each parameter employed in sensitivity analysis should be discussed based on the prior scientific knowledge or the degree of parameter variability (either estimated or known). Conservative investigations are recommended. For example, in predicting inhibitory effects of drugs on exposure of substrates for cytochrome P450 using a PBPK model, sensitivity analyses conservatively evaluating the inhibitory activities (e.g., inhibition constant Ki for reversible inhibition) are considered useful. For assumptions of key importance, sensitivity analyses assuming "worst-cases" are recommended. For parameter values with high uncertainty and known variability, their impacts on overall outcomes should be carefully assessed. Furthermore, in conducting a PBPK model analysis in a pediatric population, it is desirable to conduct sensitivity analyses for parameters concerning the maturity of drug-metabolizing enzymes and transporters involved in clearance as necessary, for assessment of uncertainty.

2.5. Results

2.5.1. Results of model qualification

Modeling results and information sufficient to demonstrate the following should be presented: (1) appropriateness of the resulting PBPK model for the objective of modeling and simulation as well as investigations of issues; (2) robustness of the model.

When the predictive performance of the PBPK model (including the uncertainty of model parameters) is not acceptable for the objective of modeling and simulation, improvement or refinement of the model should be considered (e.g., by accumulation of information such as additional data on pharmacokinetic properties). Accordingly, it is important to describe the results and information concerning model qualification with concomitant reference to limitations of the model. In addition, evaluation results on the predictive performance of the PBPK model built should be described to demonstrate that the model is capable of consistently explaining or representing actual pharmacokinetic properties of the investigational drug. If this is difficult, the model may not be applicable for simulation under a particular scenario due to the limitation of the model.

In demonstrating the robustness of the model, results of PBPK model validation

and sensitivity analyses should be clearly presented to ensure appropriate discussion concerning the model robustness. In evaluating the predictive performance, comparisons of predicted and observed data of pharmacokinetic profiles of a drug should be graphically represented as overlay plots (linear and semi-log plots). In some cases, graphical representations that allow visual comparison of distribution tendencies of observed data surrounding the predicted mean concentration time course, as well as the variability of observed data against the prediction interval of predicted data may be useful. In comparing pharmacokinetic parameters obtained from predicted and observed data, descriptive statistics, etc., should be presented as tabular data. When the predictive performance of the model for changes in blood/plasma concentration and pharmacokinetic parameters (C_{max}, AUC, etc.) tends to be poor, the impact of this tendency on investigations for which the analysis is intended for are explained with the use of figures and tables, etc., if necessary. If a sensitivity analysis is conducted for a particular parameter, the results should be described under this section. In describing results obtained from a sensitivity analysis, visual presentation using figures and tables is useful.

2.5.2. Application of models

The simulation results according to the objective of model building should be presented clearly and systematically. Pharmacokinetic parameters (C_{max}, AUC, etc.) obtained from simulation should be visually presented using figures as necessary. Parameter values should be reported as descriptive statistics such as mean, standard deviation or range, etc.

2.6. Discussion

This section should discuss the scientific validity of the PBPK model as well as its uncertainty and limitations. This section should also describe the validity of the simulation results according to the purpose of use.

The scientific validity of the PBPK model should be discussed considering information such as existing observed values. Depending on the objective of using the simulation results, it is important to consider not only the mean value of each parameter but also the magnitude of inter-ndividual variability. Concerning the results of sensitivity analyses, the impact of varying individual parameters on the simulation results should be discussed, considering the purpose of use of simulation as well as simulation conditions and expected clinical effects. The uncertainty of parameters and limitations in model application should also be discussed, and

potential effects of such limitations on the simulation results and interpretation thereof should be discussed.

In predicting changes in drug exposure by simulation with a PBPK model analysis to provide the rationale for recommendation of particular dosage and administration, it is important to consider the relationship between the drug exposure and efficacy/safety.

When the simulation results obtained from PBPK model analysis are used for decision-making in clinical development or clinical use of the drug (alternative to clinical trial data, necessity or degree of alerts in the package insert, rationale for dose adjustment, etc.), the validity of such use should be discussed, including the impact on efficacy and safety of a drug, as well as associated risks.

3. PBPK platforms

This guideline is applied to either commercially available or proprietarily built PBPK platforms. When a commercially available PBPK platform is used in a PBPK model analysis, basic information (including the name and version of the software used) should be described in the analysis report. When drug parameters and system specific parameters of a commercially available PBPK platform are used, their predictive performance needs to be verified according to the objective of analysis. In addition, if needed for a particular use, drug parameters and system specific parameters of a commercially available PBPK platform may be modified or changed. However, such modifications and changes should be clearly explained, and use of the modified and changed PBPK platform should be validated in the analysis report.

Whether a commercially available PBPK platform is used or not, information concerning system specific parameters, drug parameters, and simulation, etc., needs to be reported appropriately, based on the description in the aforementioned “2. Content of an analysis report” section of this document. The method and results of model verification are described in “ 2.4. Methods of analysis’’ or “2.5. Results’’, if necessary.

4. Electronic data submission

Concerning the PBPK analysis model subjected to electronic data (e.g., submission on application for approval), electronic data should be submitted in addition to the analysis report, in accordance with a series of relevant notifications, etc.

5. Relevant guidance and guidelines

1) PSEHB/PED Notification No. 0723-4, dated July 23, 2018 Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information

2) PMSB/ELD Notification No. 1334, dated December 15, 2000 Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11 Guideline)

3) PSEHB/PED Notification No. 1227-5, dated December 27, 2017 Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11(R1) Guideline)

4) PSEHB/PED Notification No. 1225-1 December 25, 2019 Revision of Guidance for Establishing Safety in First-in-Human Studies during Drug Development

5) PSEHB/PED Notification No. 0608-4, dated June 8, 2020 Guideline for Exposure-Response Analysis of Drugs

6) PSEHB/PED Notification No. 0318-4, dated March 18, 2020 Revision of Basic Principles on Electronic Submission of Study Data for New Drug Applications

7) PSEHB/PED Notification No. 0124-4, dated January 24, 2019 Revision of Notification on Practical Operations of Electronic Submission of Study Data for New Drug Applications

6. Glossary

- Drug parameters

Parameters depending on the drug subject to model building (e.g., physicochemical properties and pharmacokinetic properties related to *in vitro* and *in vivo* absorption, distribution, metabolism, and excretion).

- System specific parameters

Parameters depending on the physiological system and related to physiological properties of humans (e.g., organ blood flow, tissue composition, amounts of enzymes and transporters). These parameters are dependent on the population subject to simulation.

- Model verification

Process of ensuring the accuracy and reliability of the underlying mathematical code and calculations of a model.

- Model validation

Process of determining the degree to which a model is an accurate representation of the actual situation, based on simulation results. Model validation is conducted by comparison of the predicted data and observed data which is obtained under typical conditions.

- Model qualification

Process of evaluating credibility of the predictive performance of the PBPK model for a specific purpose. Based on purpose of use (applicability) and the result of model verification and model validation, this process is to be evaluated comprehensively whether it is appropriate to apply simulation results of model analysis for the purpose of use.

- Model robustness

Model robustness is to obtain consistent results for the intended use of the model within the expected fluctuation range, even with variations in uncertain model parameters.

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