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令和元年６月 19 日

各都道府県衛生主管部（局）　御中

厚生労働省医薬・生活衛生局医薬品審査管理課

「母集団薬物動態／薬力学解析ガイドライン」の英文版について

「母集団薬物動態／薬力学解析ガイドライン」については、「「母集団薬物動態／薬力学解析ガイドライン」について」（令和元年５月 15 日付け薬生薬審発 0515 第１号厚生労働省医薬・生活衛生局医薬品審査管理課長通知。以下「課長通知」という。）により貴管下関係業者等に対する周知をお願いしたところですが、今般、標記について、別添のとおり取りまとめましたので、貴管下関係業者等に対し周知方願います。

なお、本ガイドラインの正文は課長通知別添の邦文版であり、本英文版は参考資料として作成した仮訳であることに御留意ください。

PSEHB/PED Notification No. 0515-1
May 15, 2019

Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis

Contents

1. Introduction

1-1. Background and objectives

In clinical drug development, phase I clinical trials are generally conducted to evaluate the tolerability, safety and the basic pharmacokinetic profile of the drug, and to investigate the exploratory pharmacokinetics and pharmacodynamics of the drug in healthy volunteers. This is done to obtain the information needed for planning and conducting subsequent clinical trials. A patient population, however, sometimes tends to exhibit great diversity in terms of age, body weight, type and severity of disease, concomitant drugs, genetic factors, and lifestyle habits. This results in pharmacokinetic or pharmacodynamic differences when a patient population is compared to a healthy volunteer population. Therefore, an understanding of the relationship between the dose, pharmacokinetics, and pharmacodynamics through phase II and III clinical trials involving patients in whom a drug under development is indicated, clinical trials in children, elderly persons, or populations with organ disorders related to drug elimination, drug interaction studies, etc., can be useful to predict the efficacy and safety of the drug and to obtain the appropriate dosage and administration. This approach also offers useful information when considering dose adjustment in patients with a certain characteristic or using a certain concomitant drug.

Two approaches are used for the analysis of drug concentration etc. One is the standard two-stage analysis in which relevant parameters are estimated for individuals and respective statistics are performed in a second step. The other approach utilizes a population analysis where relevant parameters are estimated for the population to which the individuals belong. Population analysis makes it possible to simultaneously derive population mean values of pharmacokinetic and pharmacodynamic parameters and their variability. Furthermore, the influence of multiple relevant intrinsic and extrinsic factors (covariates) on the drug concentration and other clinical endpoints obtained from a large number of subjects with a wide range of backgrounds can be evaluated, while putting less strain on subjects by reducing the frequency of sampling in individual subjects (optimal sampling). These attributes allow population analysis to be applied in late-phase clinical trials (in the target patient population) and the pediatric drug development. Use of population analysis has recently been increasing in the investigation of pharmacokinetics and pharmacodynamics, exposure and response relationships in large-scale clinical trials that are conducted in multiple regions. With the rapid progression of globalization in drug development,

population analysis has become a valuable analytical approach in the evaluation and ethnic comparison of patient pharmacokinetic profiles and the consideration of appropriate dosage and administration.

Utilizing simulations using population analysis models helps to obtain useful information on the efficient conduct of clinical trials, taking the characteristics and development stage of the drug into consideration and with a recognition of the limitations due to the limited amounts of data and information used for the analysis, and to appropriately provide information to those involved in clinical practice.

This guideline is intended to provide general guidance that is scientifically valid at the present time so that evaluations based on population analysis are appropriately conducted during drug development, and to summarize the points to consider and the basic concept of the analysis of population pharmacokinetics and pharmacodynamics. Each contents in this document has been reviewed based on scientific knowledge at the present time, however, when new findings are obtained with the progress of research in the future both in theory and its practical application, it is necessary to act flexibly based on scientific judgments.

1-2. Scope

This guideline should be applied to the evaluation of population pharmacokinetics and pharmacodynamics for data obtained from phase I, II, or III clinical trials, post-marketing clinical trials, or clinical pharmacology studies, and/or a combination of clinical trials.

2. Study procedures

2-1. Clinical trial plan and execution

It is preferable that the sponsor of a clinical trial should take the following points into consideration in planning and conducting the clinical trial. Over the course of the process from planning of the clinical trial to evaluation of analysis results, it is important to collaborate with domain experts, such as those working in the areas of clinical pharmacology, pharmacokinetics, biostatistics and pharmacometrics.

For post-marketing clinical trials, as defined according to Article 56 (Standards for Documents Submitted in Reexamination etc.) of the Standards for the Implementation of Clinical Trials or Pharmaceutical Products (MHW Ordinance No. 28, 1997), "clinical trial"

should be replaced by "post-marketing clinical trial".

2-1-1. Points to consider prior to clinical trial planning

(1) Points to consider regarding study design

There are certain points to consider in terms of clinical pharmacology, pharmacokinetics, pharmacodynamics, biostatistics, and pharmacometrics when planning a clinical trial to obtain data for population analysis.

During population analysis, the model is built based on consideration of such factors as the objectives of the clinical trial, dosage and administration, target population, pharmacokinetics and mechanism of action, objective of the analysis, type of data collected (e.g. continuous or discrete values), and any restrictions on the collection of samples or data. For this reason, the trial is designed by taking into consideration information and study results that are already available, in addition to factors such as variable factors that may affect pharmacokinetics and pharmacodynamics, efficacy outcome measures (e.g. true or surrogate endpoints, or pharmacological endpoints that were validated for their relationship to clinical efficacy or adverse reactions, and exploratory biomarkers), safety outcome measures, timing of sampling, and sample size.

Where there are specific pharmacokinetic parameters to be estimated in population pharmacokinetic analysis, the appropriateness of sampling timing has to be considered, taking into account the accuracy of estimation of such parameters. In the case of a chemical compound with a high plasma protein binding ratio, it is also useful to ensure presence or absence of changes in the unbound fraction or unbound drug concentration can be determined.

Timing of efficacy and safety endpoint evaluations and acceptable time windows, if necessary, should be clearly described by taking the onset time of efficacy and adverse events into account. It is also important to consider the relationship between the times at which data on the drug efficacy and safety endpoints are obtained and the times at which sampling is conducted for the determination of drug concentrations so that the exposure and response relationship can be efficiently evaluated.

In case the data for population analysis are collected over a long period of time from the same subject who is continuously receiving an investigational drug, parameters such as body weight, age, renal or hepatic functions, and drug metabolizing enzyme activities, which are

inhibited or induced, may change over time. If it is necessary to evaluate changes over time in such parameters, the data of the item to be examined should be collected multiple times over time. If the investigational drug's pharmacokinetics and efficacy endpoints are expected to change significantly in a short period of time, repeated measurements of the drug concentrations and efficacy endpoints maybe useful within the same subject.

Simulations based on previous study results are useful in considering the study design, such as the timing of sampling for drug concentrations and efficacy endpoints and sample size, which are relevant to the planning of population analysis. For instance, performing simulations with various distributions and data quantity of drug concentrations and covariates makes it possible to investigate how results would be affected in advance and to reflect the results of the investigation in the future study design.

Hypothetical conditions set for the purpose of building a population analysis model strongly affect the analysis results, and it is therefore important to consider the study design thoroughly to obtain reliable estimates for parameters of interest.

(2) Points to consider in developing a data collection plan

The plan for collecting samples for the measurement of drug concentration should be clearly described. In the sample collection plan assuming population analysis, it is permitted to specify a wider range than for sample collection points of a standard pharmacokinetic study. To obtain the necessary drug concentration data for the estimation of parameters of interest, however, it is preferable to set multiple time points for sample collection so that sampling is not concentrated on a specific time point. A practical approach that can be accommodated in clinical trial environments is to allow a specific time window for sampling and to collect samples within the acceptable time windows. The actual time of sampling should be accurately recorded. In relation to time of sampling, it is fundamental to obtain accurate information on the time of dosing when performing pharmacokinetic analysis. Patient medication history before sampling, including the time of dosing, should be collected while taking into account the elimination half-life of the investigational drug being evaluated. In cases of drip infusion, the start and end time of drip infusion need to be accurately recorded.

When the effects of concomitant drug(s) are evaluated, dosing information of the concomitant drug(s) should also be obtained. It is necessary to take appropriate measures to

prevent noncompliance with treatment, as this may cause errors in the interpretation of the estimated parameters, and to also establish a system to obtain objective records on treatment compliance in reference to case report forms and patient diaries, in principle.

2-1-2. Points to be described in protocol

Regarding population analysis, points to be described in the protocol include the primary objectives of the population analysis. If it is clear that data from the clinical trial is combined with data from other clinical trials, this fact should be detailed in the protocol. If it is clear that a population analysis is to be conducted during the clinical trial and the plan for the population analysis is prepared separately from the other analysis plan, again this fact should be detailed in the study protocol.

2-1-3. Points to be described in the analysis plan on population analysis

The analysis plan should describe the objective, overall strategy, and technical aspects such as the procedures of the population analysis. Basic items to be included in the analysis plan are the study and subjects to be included in the population analysis and the rationale for selection, the method for selection of the model, the method for estimation of parameters, the software to be used in the analysis, the handling of predicted analytical issues (e.g. the handling of missing values, concentrations below the lower limit of quantification, outliers), and others. If the population analysis has more than one objective, the primary and secondary objectives should be separately presented if necessary. Whether the subjects used in the analysis include healthy volunteers or target patients, or both, or a limited population of subjects is adopted based on the ethnicity, age, or other background factors, should be determined with respect to the objective of the population analysis. In the case where the analysis starts with an existing model e.g. built for another indication of the investigational drug, or established for adults but applied to pediatrics, the facts that an existing model is used, as well as the rationale why such a model could be used should be presented. Regarding model building, the planned model building method, criteria for the inclusion of covariates in the model, methods of model diagnosis and model evaluation should be described.

Although timing of preparing the analysis plan depends on whether or not data from the clinical trial are to be combined with data from other clinical trials, the analysis plan should be developed at appropriate timing such as before the database is locked or before the start

of the analysis, considering the objective of the analysis. If it becomes necessary to perform additional analyses that are not described in the analysis plan, an analysis plan should be prepared before performing the additional analyses or the details and background of the additional analyses should be described in the population analysis report after performing the additional analyses, depending on the analysis content.

2-1-4. Points to consider related to analytical method of drug concentration

Analysis of drug concentrations should be performed using a method that has been validated in an appropriate manner according to the applicable guidelines on analytical method validation. It is preferable to use a central laboratory measurement system whereby drug concentrations are analyzed at a single facility. If drug concentrations are measured at multiple facilities, it is preferable to ensure consistency, etc. of the measured concentrations at the different facilities.

Collecting data on drug concentrations, dosing information, covariates, etc. on an as needed basis and being aware of the presence/absence of uneven data distribution, etc. help to ensure the efficient conduct of analyses rather than waiting until the time of data lock for the clinical trial. If, however, the clinical trial is being conducted in a double-blind manner, data collection on an as needed basis during the clinical trial requires appropriate measure to maintain the study blinding.

Regarding blood and other biological samples, the entire processes from the sample preparation, storage at the clinical trial site, transfer of the samples from the clinical trial site to the analytical laboratory and the analysis at the laboratory should take place in an efficient manner, by securing human resource, places, equipment, etc. For long duration clinical trials, analysis should be planned to ensure that the analysis will be completed before the expiration of the stability period of samples.

2-2. Data handling

2-2-1. Data management

To ensure the validity and reliability of the results of population analysis, it is important to manage the data for analysis, in addition to the statistical processing method which serve as a precondition, and the quality and validity of the software used. The data for analysis should be managed according to an appropriate document such as a standard operating

procedure (SOP) that stipulates operating procedures beforehand. Examples of data management flows are illustrated in Figures 1-1 and 1-2. Population analysis can be performed by combining data from multiple clinical trials. Analytical data may be developed by selecting, combining, and processing data on necessary items from individual clinical trial databases (Figure 1-1), or by selecting and processing data on necessary items from a clinical trial database in which data from multiple clinical trials are stored in the same format (Figure 1-2). In either case, specifications for analytical data should be documented in advance. It is important to ensure traceability in a series of processes of creating analytical data from clinical trial data. The adequacy of the developed analytical data should be judged through visual checking of the figures generated from the data, review of the summary statistics, etc.

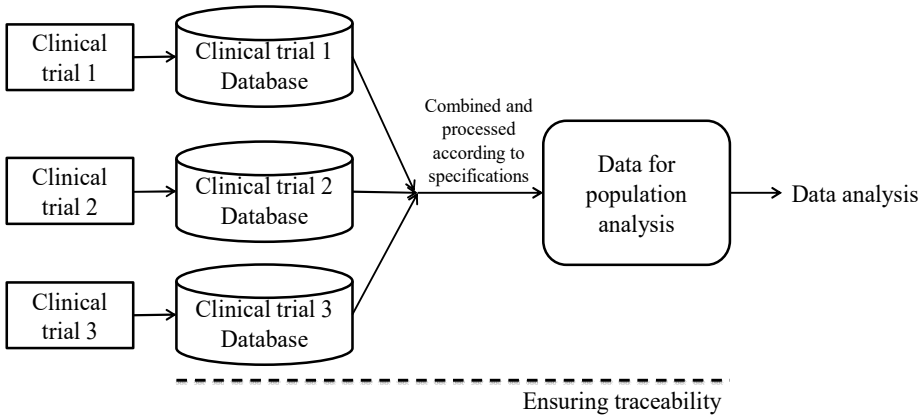

Figure 1-1 Example of analytical data management flow: where data are prepared by selecting, combining, and processing data on necessary items from individual clinical trial databases

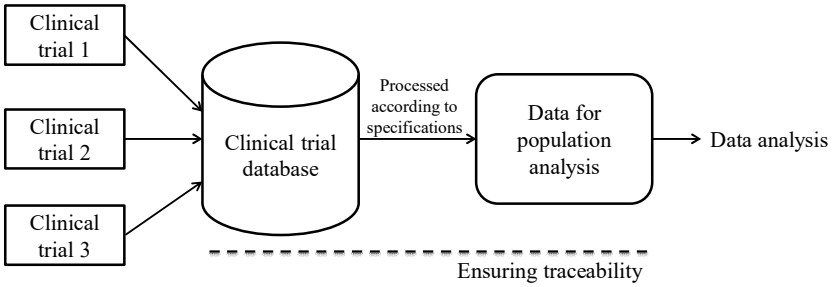

Figure 1-2 Example of analytical data management flow: where data are prepared by selecting and processing data on necessary items from an integrated database (clinical trial database)

2-2-2. Missing values

Missing values may cause bias in the estimations, which in turn may lead to false conclusions, therefore every effort should be made to minimize missing values. Missing values occur when some of the covariate data are missing or the measurement values of drug concentrations and clinical responses are missing. In either case, this may complicate interpretation of the analysis results. Any issues that may occur as a result of missing drug concentration values, clinical response values and covariate data values and how to handle them, should be described in advance in the analysis plan. In addition to such a policy considered in advance, sensitivity analysis, etc. may be performed as necessary to investigate consequences of missing values.

2-2-3. Concentration values below the lower limit of quantification

The simple omission of values for concentrations below the lower limit of quantification (LLOQ) from the analysis data may result in biased parameter estimates. An appropriate method of handling of values for concentrations below the LLOQ in population analysis

should be selected based on considerations of the characteristics of the analysis data or the objective of analysis.

2-2-4. Outliers

The definition of outliers and the strategy for handling of outliers should be clearly defined in the analysis plan as far as possible. It should be discussed how outliers can affect the results, based on comparison of results including/excluding outliers, and the discussion should be described in the population analysis report. If analysis is performed by excluding outliers, the rationale for the decision should be explained from the standpoints of physiological and clinical trial-related events, etc.

2-3. Model building and diagnosing

Population analysis is an iterative process of repeated model building and model diagnosis. The type and level of the diagnostic method to be applied are selected appropriately based on the stage of analysis. New techniques to analyze, build and diagnose population models are being studied and developed on a regular basis. Those who conduct analysis are required to have correct understanding of the algorithms used and to consider thoroughly the appropriate techniques to be used at different stages of the population analysis.

A typical method of model building and diagnosing is explained, as well as an example of population analysis flow in Figure 2.

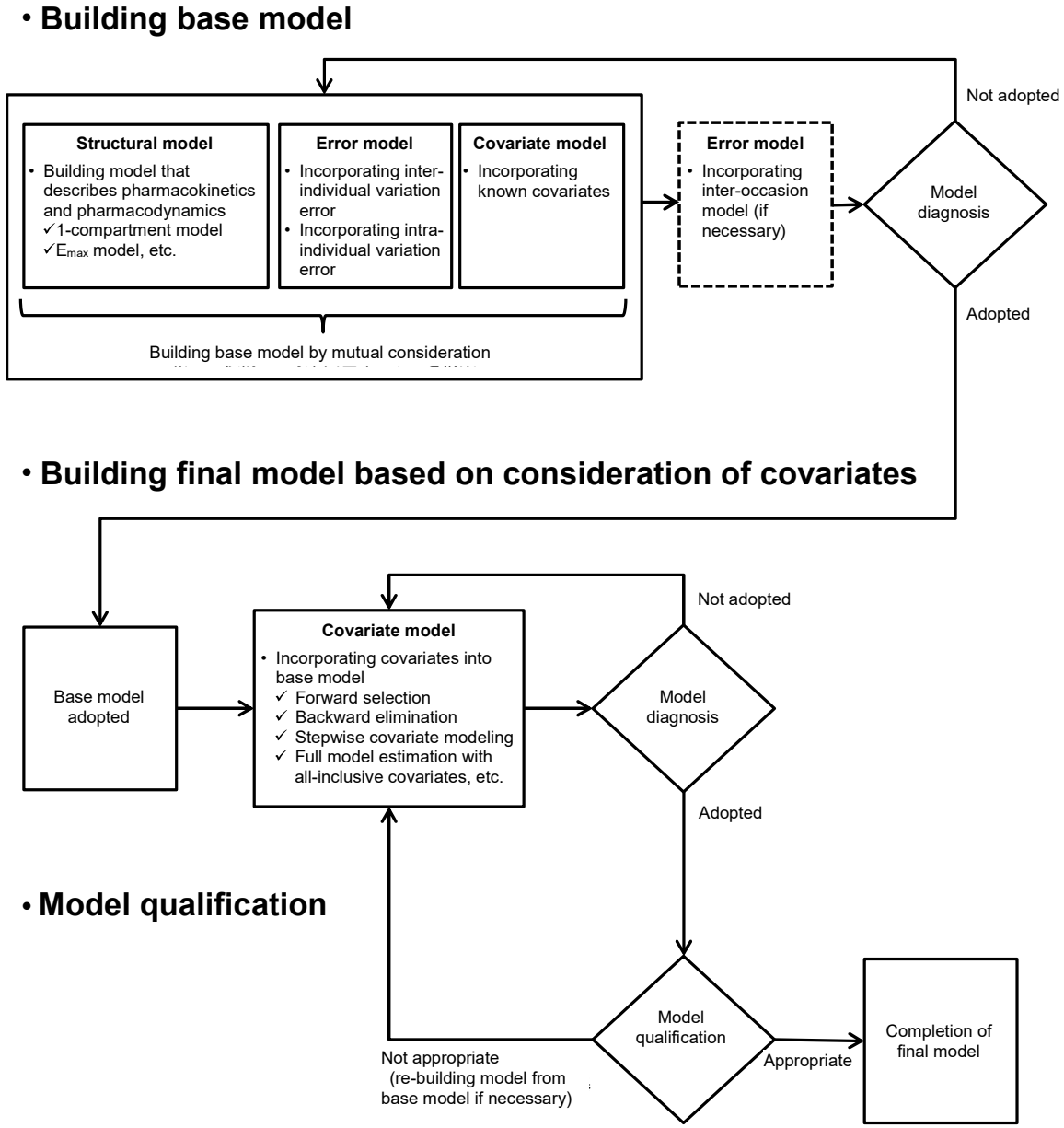

Figure 2 Example of population analysis flow

2-3-1. Building population pharmacokinetic and pharmacodynamic models

A population pharmacokinetic or population pharmacodynamic model may be referred to as a base model or a final model, depending on the stage of model building. A base model consists of a structural model, inter- and intra-individual variability (error model), and covariates (covariate model) that clearly affect pharmacokinetics / pharmacodynamics. The final model is a model that incorporates important covariates into the base model, and is obtained after evaluating its validity.

In the following, structural, error, and covariate models are explained, although there is no need for the process of building a model to follow this order. It is important to present the process of analysis, the path leading to the conclusion, and the rationale for selecting a certain model from among multiple different choices, to ensure that retrospective investigation is possible and the analysis results can be reproduced in an objective manner.

(1) Structural model

A structural model is a model to describe pharmacokinetics and pharmacodynamics, including models such as a compartment model and E_{max} model. The first point to consider in selecting a structural model is to select one that can appropriately represent the characteristics of observations. The characteristics include linear or non-linear pharmacokinetics, and monophasic or polyphasic behaviors. Furthermore, when selecting a structural model, the amount of information in the obtained data needs to be considered. For instance, pharmacokinetic parameters for the absorption phase cannot be estimated from the drug concentration data obtained from samples collected only during the elimination phase.

Where distinction between linear and non-linear models and the optimal number of compartments is concerned, results of clinical pharmacokinetic studies conducted at an early stage, such as phase I clinical trials, often serve as reference. However, model selection, the number of compartments in particular, depends on the sampling frequency and schedule, and it does not necessarily have to match the results obtained in previous studies. Setting too many parameters as compared to the characteristics of the obtained data should be avoided, a simplified model may often be more appropriate where the analysis is to be performed based solely on a small number of drug concentrations collected from individual patients. On the other hand, simplifying a structural model may not be required if the analysis is to be performed based on drug concentrations obtained from intensive sampling in a phase I clinical trial, combined with the drug concentrations obtained from sparse sampling in a phase II or later clinical trial.

(2) Error model

In general, population analysis involves building of a model by setting two error terms, inter- and intra-individual variability.

If inter-individual variability is described parametrically, the generally used types of error

distribution are normal and lognormal distributions. The former is also called an absolute error model, and the latter corresponds to a proportional error model. As for intra-individual variability, in addition to absolute and proportional error models, a mixed type, or a combination of the two, is also used. In other words, it is assumed that data for low-concentration areas have a certain variance, while high-concentration areas have errors proportional to the concentration included in the measurement data. The appropriate error model is decided based on model diagnosis such as an examination of the distribution of parameter estimates, consideration of the analytical methods used in measurements, various residual plots, and so on (model diagnosis is described in detail in Section 2-3-2).

If there are correlations observed between multiple inter-individual variability parameters, such correlations may be incorporated and analyzed in an appropriate manner. However, there are cases where an apparent correlation is observed as a result of influence factors that are important as covariates being missed, and it is necessary to examine error and covariate models in a mutual manner. Inter-individual variability parameters should be characterized for structural parameters that allow for the estimation of inter-individual variability based on data.

In addition to the inter-individual variability and intra-individual variability, inter-occasion variability for individual parameters may also be taken into account in some cases. In such a case, three error terms, inter-individual, intra-individual, and inter-occasion variability should be set in a model.

(3) Covariate model

In population analysis, building of an appropriate covariate model leads to the identification of contributory causes of inter-individual variability. Selection of covariates should take account of factors considered important from pharmacokinetic and clinical standpoints.

Covariates to be incorporated into a model depend on the distribution of observed covariates. For instance, if all subjects have normal renal function, a relationship between renal function and clearance cannot be obtained, even for drugs that affect renal excretion. In an analysis of correlation with pediatric development, the reliability of the analysis result is low unless data are obtained from subjects that are evenly distributed in each age group. An analysis of a special factor generally requires the formulation of a study protocol that

ensures that data suited to the objective of the analysis are collected.

When building a base model, it may sometimes be appropriate to incorporate apparent covariates that affect the pharmacokinetics and pharmacodynamics into the structural model in advance. For instance, in a case of a drug for which the dose is determined based on the body surface area, incorporating the body surface area into clearance helps obtain results more suitable for clinical application. The methods of selecting covariates utilized in the final model building process in a nonlinear mixed-effects model include forward selection, backward elimination, stepwise covariate modeling, full model estimation with all-inclusive covariates, and so on. Other methods may also be used as long as an appropriate covariate model may be built in a reasonable manner according to the algorithms used.

When selecting covariates, correlations between different covariates such as “advanced age” and “reduced renal function” require attention. Basically, the effect of covariates on independent factors should be investigated through analyses. When multiple factors to be considered as covariates have a strong correlation, it is preferable to build a model by selecting factors that are more physiologically and clinically appropriate from the correlating factors. If two covariates with a strong correlation are included in the dataset, investigation should be undertaken to see if an analysis that incorporates the influence of a covariate at the same time does not lead to unstable results, such as significant differences in analysis results due to differences in the initial values and analysis datasets, or no convergence. Covariates that are more physiologically and clinically appropriate and are easy to use in healthcare settings should be selected. It is therefore necessary that the selection of covariates should be based on clinical, pharmacodynamic, and pharmacokinetic knowledge and discussions, coupled with a valid statistical evaluation, rather than being based solely on statistical significance.

2-3-2. Diagnosis of the validity of a model

After being built, a model should be diagnosed for its validity from the standpoints of the stability and robustness of the analysis results, the plausibility of the parameter estimates obtained, and predictive performance for reproduction of analyzed data. As the “valid model” is necessarily determined by the purpose of the analysis, criteria for diagnosing the validity of a model cannot be unambiguously defined. To objectively clarify the validity of the constructed model, it is necessary to perform appropriate diagnoses according to the

objective.

The stability and robustness of the analysis results may be diagnosed by investigating the effects of the initial parameter values, the effects of the hypothesis or conditions used for model building, the effects of excluding individuals with observations or covariate data deviating from average trends, and so on. Observations and individuals that may have a significant impact on the results may be identified by their effects on the objective function value, for instance. Acceptably small estimation error of each parameter estimate may also be another piece of information to judge the stability and robustness of the analysis result. In addition, confidence intervals estimated by such methods as bootstrap, jackknifing, and likelihood profiling, etc. are useful to judge the stability and robustness of analysis results. Concerning diagnosis methods from which confidence intervals are derived, the bootstrap method generates a dataset by randomly resampling individual data from the original dataset used for the analysis, obtains summary statistics of estimates by repeating the process for obtaining parameter estimates, and compares these with the original parameter estimates to evaluate bias and precision. In general, bootstrap statistics are obtained based on a summary from the runs with successful convergence. When there is a considerable number of bootstrap runs with abnormal termination, the cause of abnormal termination and its consequences should be examined.

Plausibility of parameter estimates, in general, can be comprehensively diagnosed by visual inspections of agreement between model estimates and observations, dependency of residual errors on elapsed time from administration or estimates, and, model dependency of post hoc estimates of inter-individual parameters on time, dose amounts, or primary covariates, dispersion or skewness of inter- or intra-individual variability, and outliers, as well as the clinical, pharmacodynamic, and pharmacokinetic validity. It is necessary to note that random effects which are excessively small and close to zero may suggest a lack of sufficient information with regard to the inter-individual variability. It is also necessary to check the presence of shrinkage, where individual post hoc parameter estimates converge on the population mean due to insufficient information. Care needs to be taken for evaluating any parameter-covariate relationships with large shrinkage found in the random effect on the parameter.

For visual evaluation of predictive performance of the model, visual predictive check (VPC), a simulation-based evaluation model taking inter-individual variability and intra-

individual variability into account, is used. The model simulates model predictive values corresponding to the analysis dataset based on the parameter estimates. By superimposing the median and appropriate percentile intervals on the plot of actual observations, visual evaluation is performed. The validity of the structural model or random effect model for inter- and intra-variability is evaluated by comprehensively taking evenly distributed observations relative to the predicted median and the ratio of observations contained in the prediction intervals into account. It is necessary for appropriate visual comparison to suitably set the percentiles and bins for constructing prediction intervals. When groups with different doses or primary covariates are evaluated simultaneously, prediction corrected VPC, etc. should be considered, although evaluation of predictive performance by each factor by creating individual VPC plots by group stratified for dose or primary covariates may derive more useful information in some cases.

Predictive performance may be evaluated on a dataset that has not been used in the model building (i.e. validation dataset) to rigorously ensure predictive performance on data obtained from the same population (external validation method). It is, however, associated with certain problems including a reduced amount of data available for model building as a result of data-splitting and the potential uncertainty of the evaluation due to a single round of data-splitting. To compensate for these shortcomings, cross validation techniques can be used, whereby rounds of data-splitting, model building and predictive performance are conducted repeatedly. With this method, repeating of a series of processes avoids some of the risk of making an erroneous decision where an extremely biased distribution of validation data is used for predictive performance, and it also increases the size of data to be used for model building.

2-4. Model qualification

Model qualification is conducted to ensure that the established population final model has sufficient performance characteristics to satisfy the purpose of the analysis from an objective viewpoint based on the results of model diagnosis. As is true of model diagnosis, there is not a general evaluation method that is applicable to all analyses, and it is therefore necessary to determine an appropriate form of multiple model diagnosis and standards that are required for practical purposes for each analysis based on the characteristics of the drug, from clinical, pharmacodynamic, and pharmacokinetic viewpoints. It is also necessary to report the results

of the chosen model diagnosis method to verify that the model eventually adopted is an appropriate population final model.

3. Model application

The final model built by population analysis and parameter estimates imparts useful information for setting an appropriate dosage and administration and may also become useful information for the proper use of drugs. In addition, they may be utilized to estimate the pharmacokinetic or pharmacodynamic behavior in a certain target population and to plan clinical trials. Points to consider for model application are outlined below.

3-1. Predicting pharmacokinetic or pharmacodynamic characteristics of a certain target population

If a covariate included in a population model is a factor that describes characteristics of a certain target population, it may be useful to investigate the pharmacokinetic or pharmacodynamic profile in the target population by simulation incorporating error models. It is necessary to consider that, extrapolation by simulation beyond the distribution of covariate in the target population can reduce the reliability of the predicted values as they are obtained from the tails of the covariate distribution.

3-2. Clinical trial design

Prediction of the clinical trial results through stochastic simulation that takes into account information such as inter- and intra-individual variability and expected distribution of covariates in the patient populations in the target clinical trial may be useful in developing a study plan. For instance, planning and decision-making for a phase III clinical trial may have benefit of higher levels of certainty by adding model analysis and simulation based on the pharmacokinetic and pharmacodynamic data up to the phase II clinical trial combined with the results of analysis of the observations obtained from the phase II clinical trial. As simulation involves variety of approximation and assumptions, it is necessary to investigate the assumptions used as the premise of the model building, background of the target population, and prognostic factors for the target disease in advance, and that there are inherent limitations due to the small amounts of data and information used in the analysis.

In creating simulation data that contain covariates (simulation target population), attention

should be made to correlation between covariates. In the case of parametric sampling in which the mean and estimates of variance of the covariates adopted are used for sampling of random numbers based on probability distributions such as normal and uniform distribution to generate new data, sampling based on estimated distribution of limited amounts of data can cause prediction bias. There are also possibilities that covariance between parameters and interaction between parameters and covariates may not be reproduced appropriately.

4. Reporting and providing information

4-1. Population analysis report

The population analysis report should be prepared in accordance with the descriptions in the analysis plan for population analysis. It is desirable that the population analysis report contains the particulars outlined below. However, simplified population analysis report may be appropriate in some cases, such as where the results of population analysis are included in the clinical study report, or depending on the objective of the population analysis. When the analysis results are to be used for regulatory submission, it is necessary that quality control and assurance for the data management, analysis and the report should be conducted in an appropriate manner.

1) Summary

A concise overview that summarizes the population analysis should be presented. The objective of analysis, methods, results, and sufficient information to explain the key conclusions should be included in the overview.

2) Introduction

In the introduction section, concise descriptions of background information of the investigational drugs, and the positioning of the present analysis in the development of the investigational drugs should be provided.

3) Objective of population analysis

The objective of the population analysis should be stated. If there is more than one objective, it is desirable that primary and secondary objectives be explicitly stated.

4) Method of population analysis

The overall methods such as clinical trials covered by population analysis, data used in analysis, and methods of data analysis should be described as described below. Any change

from the analysis plan should be indicated.

- Clinical trials covered by population analysis

The clinical trials covered by population analysis should be identified, and then concise descriptions of each of the clinical trials should be provided, including the study designs and contents, target subjects and number of subjects, characteristics of subjects, investigational drugs, and their dosage and administration.

- Data used in analysis

Descriptions of the drug concentration and other clinical endpoints investigated in the population analysis, information on the data collection for drug concentrations and efficacy endpoints, including number of sampling points, sampling times, and endpoint measurement times, and variables investigated as covariates in the population analysis should be provided. For derived covariates such as creatinine clearance, the calculation method used should be presented. Handling of missing data, values for concentrations below the LLOQ, and outliers should be described.

- Methods of data analysis

Particulars about the population analysis should be provided, including the method used, software and its version, compiler, operating system (OS) and other operating environment information, estimation method, information concerning components of the model and relevant assumptions, such as parameters and distribution of random effects, overall model building methods, covariate model building procedures (stepwise covariate modeling, full model estimation with all-inclusive covariates, etc.), selection criteria for covariates (such as p value), and the methods for model diagnosis and model qualification.

5) Analysis results

As the analysis results, the following, accompanied by a summary using appropriate figures or tables should be described.

- Characteristics of population and data as target of analysis

The number of subjects, number of data measured, time-drug concentration plots, profile of data measured, summary statistic of demographic variables and other covariates, results of handling of outliers and missing values, and so on.

- Results of model building

The process of reaching a decision on the final model, showing the rationale for the decision clearly, the parameter estimates with their standard error and diagnosis plots for the

base and final models. As for covariate selection, it is desirable to illustrate them by presenting plots that show the correlation between covariates and plots of the empirical Bayes estimates of the parameters versus covariates. The results of model qualification for the final model should be presented.

6) Discussions and clinical applications

The validity and clinical significance of the model building and estimates should be discussed. If the final model that has been built is applied to administration planning or other purposes, it is recommended that the results of simulation based on the final model as well as its reliability be illustrated in figures.

7) Appendix

A report including model files describing the structures of the base and final models and their outputs, and the datasets used in the analysis (the representative portion of the dataset for a few selected subjects may be used) should be attached as an appendix. Figures and tables not used in the main part of the report may be included in the appendix.

4-2. Regulatory submission

When the results of population analysis are used for regulatory submission, the population analysis report should be provided and Section 2.7, Clinical Summary, of the Common Technical Document (CTD) should be prepared based on the population analysis report, according to a series of relevant notifications, etc. In the clinical summary, the following information should be described; the analysis data, model building procedures, final models for pharmacokinetics, pharmacodynamics or exposure and response relationships, population parameter estimates obtained, the results of simulation performed based on the model, using figures and tables, and the model diagnosis and qualification results. Information on the population analysis should be appropriately reflected if necessary in the description of the pharmacokinetic and pharmacodynamic profiles of the drug in the relevant sections of the CTD.

For population analysis for which electronic data are subject to submission in filing for approval, electronic data should be submitted according to a series of relevant notifications.

4-3. Providing information in package insert

When the results of population analysis provide useful information for appropriate use of

the drug, population analysis information should be included in the "Pharmacokinetics" or other appropriate sections of the package insert. When the simulation results provide rationale for the important caution, descriptions of caution should be included in an appropriate part under the "Precautions" section of the package insert, indicating that the "Pharmacokinetics" section should be referred to.

When preparing these descriptions, information should be provided with the prospect that the population analysis results will be used in healthcare settings, for example, when information on pharmacokinetics in the target patient population of the drug is provided, when information on pharmacokinetic or pharmacodynamic variable factors is provided, or when information that serves as the rationale for dose adjustment for a certain target population is provided.

5. Relevant guidelines and documents

This guideline shows the general guidance that is scientifically plausible for conducting population analysis. While guidelines and documents that have already been notified provide descriptions regarding population analysis, this guideline integrates and organize contents of such guidelines, and furthermore, incorporates the latest knowledge and concepts as of present.

ICH guideline

1) PAB/PCD Notification No. 227 March 20, 1995 Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)
2) PFSB/SD Notification No. 0328007 March 28, 2005 Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D)
3) PFSB/ELD Notification No. 0916001, PFSB/SD Notification No. 0916001 September 16, 2005 Pharmacovigilance Planning (ICH E2E)
4) PAB/PCD Notification No. 335 May 1, 1996 Structure and Content of Clinical Study Reports (ICH E3)
5) PAB/PCD Notification No. 494 July 25, 1994 Dose-Response Information to Support Drug Registration (ICH E4)
6) PMSB Notification No. 739 August 11, 1998 Handling of Data on Clinical Trials on Drugs Performed in Foreign Countries, Attachment PMSB/ELD Notification No. 672 Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5)
7) MHLW Ordinance March 27, 1997 Guideline for Good Clinical Practice, Attachment PAB Notification No. 430 Enforcement of the Ordinance Regarding Good Clinical Practice (ICH E6)
8) PAB/NDD Notification No. 104 December 2, 1993 Studies in Support of Special Populations: Geriatrics (ICH E7)
9) PMSB/ELD Notification No. 380 April 21, 1998 General Considerations for Clinical Trials (ICH E8)
10) PMBS/ELD Notification No. 1047 November 30, 1998 Statistical Principles for Clinical Trials (ICH E9)
11) PMSB/ELD Notification No. 1334 December 15, 2000 Clinical Investigation on Medicinal Products in the Pediatric Population (ICH E11)

12) PFSB/ELD Notification No. 0109013 January 9, 2008, PFSB/SD Notification No. 0109002 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories (ICH E15)
13) PFSB/ELD Notification No. 0707-3 July 7, 2009 Partial Revision of the Notification Concerning Materials to Be Attached to the Approval Application Form upon Approval Application for Marketing of New Drugs (ICH M4 and M8)
14) PSEHB/PED Notification No. 0118-1 January 18, 2018 Genomic Sampling and Management of Genomic Data (ICH E18)
15) PSEHB/PED Notification No. 1227-5 December 27, 2017 Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11 [R1])

Regional guidelines and documents

1) PFSB/ELD Notification No. 796 June 1, 2001 Note on Clinical Pharmacokinetic Studies of Pharmaceuticals
2) PFSB/ELD Notification No. 0928010 September 28, 2007 Basic Principles on Global Clinical Trials
3) PFSB/ELD Notification No. 0711-1 July 11, 2013 Guideline on Bioanalytical Method Validation in Pharmaceutical Development
4) PFSB/ELD Notification No. 0401-1 April 1, 2014 Guideline on Bioanalytical Method (Ligand Binding Assay) Validation in Pharmaceutical Development
5) PFSB/ELD Notification No. 0620-6 June 20, 2014 Basic Principles on Electronic Submission of Study Data for New Drug Applications
6) PFSB/ELD Notification No. 0427-1 April 27, 2015 Notification on Practical Operations of Electronic Study Data Submissions
7) PSEHB/ELD Notification No. 1225-10 December 25, 2015 Guideline for Pharmacokinetics and Pharmacodynamics of Antimicrobials
8) PSEHB/ELD Notification No. 0723-4 July 23, 2018 Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information

Regional guidelines and documents (package inserts)

1) PSEHB Notification No. 608-1 June 8, 2017 Instructions for Package Inserts of Prescription Drugs, etc.

2) PSEHB/SD Notification No. 608-1 June 8, 2017 Points to Consider regarding the Instructions for Package Inserts of Prescription Drugs, etc.

Overseas guidelines and guidance

1) FDA: Guidance for Industry: Population Pharmacokinetics (1999.2)
2) FDA: Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications (2003.5)
3) FDA: Guidance for Industry: End- of-Phase 2A Meetings (2009.9)
4) FDA: White Paper: Challenge and Opportunity on the Critical Path to New Medical Products (2004.3)
5) FDA: Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (draft, 2014.12)
6) EMA: Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (2007.7)
7) EMA: Guideline on reporting the results of population pharmacokinetic analyses (2008.1)
8) EMA: Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (2017.2)

6. Glossary

Chapter 1

1) Population analysis: An analysis method to describe the pharmacokinetic and/or pharmacodynamic properties of a drug for a typical individual (i.e. fixed effects) and, in addition, the variability in the population (i.e. random effects).

Chapter 2

2) Structural model: A mathematical model to describe pharmacokinetic or pharmacodynamic responses.
3) Inter-occasion variability: Variability arising from changes in parameters for a subject during the evaluation period. It is generally modeled as a random effect between periods.
4) Intra-individual variability / Within-subject variability: Variability arising from changes in parameters within a subject. It may be modeled as a fixed effect dependent on period or covariates, or as a random effect between periods (i.e. inter-occasion variability). Where intra-individual variability is not modeled, it will not be distinguished from residual variability.
5) Inter-individual variability / Between-subject variability: Variability arising from changes in parameters between subjects. It is variability from the population mean parameter which is usually modeled as a random effect.
6) Outlier: For pharmacokinetic or pharmacodynamic observation: an observation that appears to be largely outside the expected distribution derived from the model. For a covariate of an individual: a value that appears to be largely outside the expected sampling distribution of the covariate in the population.
7) Covariate: A factor that has influences over pharmacokinetic and pharmacodynamic responses. Covariates include a subject's intrinsic factors (such as body weight, sex, or age) and extrinsic factors (such as concomitant drugs or smoking status) of the subject, conditions of the drug treatment (such as formulations, dosage and administration, and dietary conditions), or other factors that potentially influence the response.
8) Sensitivity analysis: In population analysis, sensitivity analysis primarily refers to an investigation of the dependence of analysis results on changes in data or parameters for the purpose of evaluating the stability and robustness of the model.

9) Base model: The structural and statistical model that best describes the data usually in absence of covariates, which is typically established before covariate exploration.
10) Final model: The model that provides the best overall description of the data and that appropriately addresses the objectives of the analysis. Typically, it is a model that has been established as a result of covariate model building based on the base model.
11) Error model: A model that describes variability from a population mean or model estimate, such as inter- or intra-individual variability.
12) Residual error: Difference between the observation and model estimate for pharmacokinetic or pharmacodynamic responses.
13) Individual parameters: The estimates of each subject's parameter set given the model parameters and the data, obtained after the estimation of the fixed effect parameters by empirical Bayes estimation conditional on a fitted model. They are also called empirical Bayes estimates or post hoc parameter estimates.
14) Forward selection: A method of covariate exploration where each parameter-covariate combinations is added in turn as a predictor for a parameter in the base model. The covariate that gives the best fit of the data according to some criteria is retained and taken forward to the next step. In the following steps all remaining covariates are tested until no more covariates meet the pre-defined level of statistical significance for being included into the model.
15) Backward elimination: A method of covariate exploration where each parameter-covariate combination is removed in turn one at a time in ascending order of effect from the full model involving all the covariates that have been preliminarily selected. The process is repeated until the effects of all of the covariates contained in the model meet the pre-defined level of statistical significance for being retained into the model.
16) Stepwise covariate modeling: A method of covariate exploration where tests are run sequentially by adding and removing covariates based on a pre-defined statistically significance level to obtain the final covariates.
17) Full model estimation with all-inclusive covariates: A method of covariate exploration where the influence on population parameters of pre-defined covariates of interest is evaluated simultaneously in the base model that involves all the covariates. The degree of the effect of a covariate is determined based on the confidence interval for the estimated effects by the covariate.

18) Bootstrap: A method to evaluate estimation errors and biases of parameter estimates for model diagnosis and model evaluation. Bootstrap datasets are generated by repeatedly resampling individuals with replacement from the original data. The model is then fit to each bootstrap dataset to obtain the sampling mean and distribution of the parameter estimates of the model.
19) Random effect: The stochastic component that describes the deviation from the typical parameter value or response.
20) Shrinkage: A phenomenon in which post hoc individual parameters (empirical Bayes estimates) shrink around the population mean (η-shrinkage) or the distribution of residual error shrinks toward zero (ε-shrinkage), due to excessive random effect parameters.
21) Predictive check: A simulation-based evaluation method used for a comprehensive evaluation of the predictive performance of a model. It may be used for a comparison with observations or the verification of consistency in properties between observed and model derived data in a visual manner (i.e. visual predictive check; VPC), for a numerical comparison (i.e. numerical predictive check; NPC), or for a statistical comparison (i.e. posterior predictive check; PPC), etc.
22) External validation: One of the most rigorous methods for model diagnosis. The predictive performance of the model obtained by using a dataset that is based on data from other studies but not used in the model building is evaluated. On the other hand, a method of reusing the data used for model building by means of division and resampling and then evaluating the predicting performance of the model obtained is called internal validation.
23) Cross validation: An internal validation method used for model diagnosis, in which a model is built based on an index dataset obtained by data-splitting, while the predictive performance of the model is evaluated using the remaining validation dataset. The process is repeatedly performed.

Chapter 3

24) Parametric sampling: Generates parameters or observations by using random numbers based on the probability distribution obtained from the estimates of mean and variance.

25) Stochastic simulation: Simulation that generates random numbers and obtains the distribution of parameters of many subjects while factoring in errors.