事　務　連　絡
令和２年６月８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

「医薬品の曝露-反応解析ガイドライン」の英文版について

「医薬品の曝露-反応解析ガイドライン」については、「「医薬品の曝露-反応解析ガイドライン」について」（令和２年６月８日付け薬生薬審発 0608 第４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願います。

Provisional Translation

PSEHB/PED Notification No. 0608-4
June 8, 2020

Guideline for Exposure-Response Analysis of Drugs

Contents

1 Introduction

1.1 Background and objectives

In drug development, investigation of the relationship between exposure and response, in addition to investigation of the relationship between dose and response (mainly efficacy or safety), is important to obtain useful information to determine the dosage and administration more efficiently in clinical studies at each stage of development, to build the study design, and to provide information to those involved in clinical practice. Developing models based on the relationship between exposure and response from an early stage development, then the results of exposure-response analyses using an updated model based on new data and scientific findings obtained from each development stage are expected to be used for quantitative decision-making that contributes to strategy planning of the next phase of development, and exposure-response analysis is therefore widely used in drug development. In recent years, it is expected that analyses of the exposure-response relationship and subsequent simulations of clinical responses based on results of the analyses will contribute to improve the likelihood of success in confirmatory studies in various disease areas. In addition, it is expected that exposure-response analyses will be further utilized as one of the methods for estimating the proper dosage and administration from limited clinical study results, as well as avoiding the conduct of unnecessary clinical studies for the development of medicinal products targeted for populations and diseases for which clinical studies are not feasible, as represented in children and orphan diseases.

The purpose of this guideline is to show a basic concept and points to consider when investigating the relationship between exposure and response as general guidance that is scientifically valid at present, so that exposure-response analyses and their utilization can be implemented properly for drug development. Points to consider concerning the descriptions related to exposure-response analyses in application materials to be submitted at the time of a market approval submission are also mentioned. Each item listed in this document has been examined based on the current scientific knowledge; however, if new knowledge is obtained with the future progress of research in theories and applications, it is necessary to act flexibly based on scientific judgment.

In addition, this guideline is intended to promote common understanding among drug developers, healthcare professionals involved in clinical trials, and regulatory authority personnel, etc. who are involved in consideration using exposure-response analyses and the interpretation of the results thus obtained, and to recommend the appropriate implementation of exposure-response analyses during drug development.

1.2 Scope

This guideline should be applied to exposure-response analyses based on the results of individual clinical studies or those generated from the integration of results from multiple clinical studies for drug development. Exposure-response analyses are performed for various reasons from an early stage of development, and discussion concerning the clinical study design, etc. in clinical trial consultations, etc. is anticipated between drug developers and regulatory authority personnel. This guideline describes the usability of exposure-response analyses in each clinical development phase, as well as examples of exposure-response analysis utilization throughout drug development. However, this guideline does not define novel requirements for drug development or market approval submissions.

In this guideline, "exposure" is used as a broad term encompassing drug concentration in plasma and other biological fluids or various pharmacokinetic parameters (AUC, C_{max}, C_{trough}, etc.).

2 Exposure-response relationship in drug development

2.1 Exposure-response evaluation

2.1.1 Dose-exposure-response relationship (see also Appendix 6-1)

The relationship between dosage and response after administration of a drug is described as the relationship between the dose, exposure observed as systemic drug concentration or drug concentration at the site of action, and the pharmacodynamic effect caused by exposure to the drug and the resulting efficacy or safety (Figure 1).

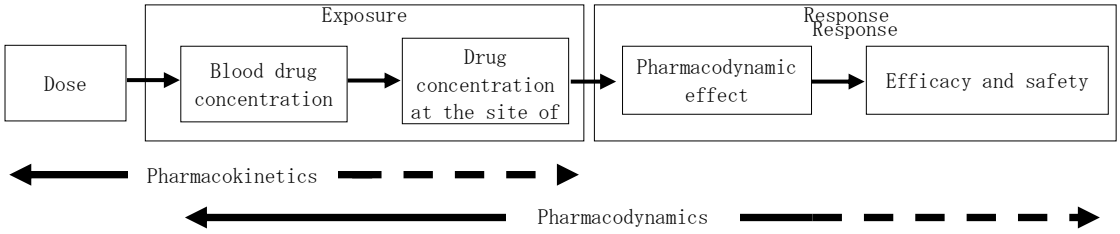


Figure 1 Relationship between dose, exposure, and response

Building a model that reveals these dose-exposure-response relationships is useful for the quantitative assessment and prediction of responses based on exposure. That is, understanding and illustration of the dose-exposure-response relationship using models are useful to explain the cause of differences in responses due to differences in exposure by inter-individual variability during the course of absorption, distribution, metabolism,

and excretion, or other differences in responses noted despite similar exposure. However, since models tend to depend on the characteristics of a drug and the data and assumptions used to construct the model, it is important to use data in line with the scope of use and purposes of the model when examining exposure-response relationships. Regarding prediction using models, it should bear in mind that prediction reliability differs greatly between a prediction within the range of existing data and prior information and a prediction that is out of the range of existing data and prior information. In addition, if the dose-exposure-response relationship is already clarified by existing clinical data, useful information may be provided to facilitate a more rational development strategy when estimating the dosage and administration for new indications or response in other patient groups.

Furthermore, consideration of the dose-exposure-response relationship lead to grasp and understand the efficacy and safety of a drug more precisely than if only the dose-response relationship is considered. When analyzing data on exposure-response relationships, it is important to use response-related data in an appropriate range of exposure according to the purpose.

2.1.2 Study design and exposure-response relationship

When performing a model analysis to clarify the exposure-response relationship, the analysis set for the analysis of the endpoint defined in line with the study objective that was prespecified in the protocol, measures to be evaluated and the summarization method, handling of interim events such as dropouts and missing data on observed values, and the method of missing data imputation should be considered based on the design of the clinical study subject to analysis. Therefore, when planning a clinical study, it is important that persons in charge of the exposure-response relationship (clinical pharmacologist, pharmacometrician, etc.) have discussion with clinician and biostatistician and other relevant people who are involved in the study, and clarify the rules on the handling of covariates, prognostic factors, confounding factors, missing values, etc. related to the exposure-response relationship before developing the analysis plan.

An analysis plan for exposure-response analysis should be prepared at an appropriate time before the start of analysis. Regarding points to require attention when preparing an exposure-response analysis plan, please refer to the relevant section of the Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis.

2.1.3 Data for analysis

The reliability of the data obtained from the analysis set to be analyzed that is used for

the evaluation of exposure-response relationship has an influence on its predicting performance. It is therefore important that the data representing the group to be analyzed should be data with guaranteed reliability that were obtained from a study appropriately and adequately managed in compliance with various laws or guidelines.

Criteria on inclusion/exclusion of data used for analysis should be determined prior to analysis and specified in appropriate documents. Regarding points to consider when collecting data on drug concentration as a measure of exposure, as well as data on efficacy measures and safety evaluation as a measure of response, please refer to the relevant section of the Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis.

In interpreting the results of exposure-response analysis, it is preferable that the analysis set which is used for evaluation of the exposure-response relationship is the same as the full analysis set in the protocol. Data to be analyzed that are used for model-based exposure-response analysis may not exactly match the data used for statistical analysis due to the fact that exposure-related data are missing because no blood sampling was performed, etc. If these analyses yield different interpretations, consideration of the differences in the composition of each dataset and their influence is useful to understand the results.

Occasionally, the exposure-response relationship can be detected more accurately by selecting a specific subject groups and analyzing, but it should be carefully interpreted as there is a possibility that a different exposure-response relationship than that from the entire population is obtained. Data from subjects who received a placebo and baseline data are useful to understand changes over time in the response measures when the drug is not administered, to grasp the distribution of the response measures in the analysis set, or to analyze the placebo effect, etc.

In general, when the exposure-response relationship is modeled by integrating results from multiple clinical studies conducted through clinical development, it is necessary to explain the validity of such integration by reviewing the comparability of the studies, the possibility of their integration, and the differences in populations and assessment measures among the studies in the analysis reports.

2.1.4 Exposure measures

The measures of exposure are selected in consideration of the relevance to response such as efficacy and adverse events, pharmacokinetic features, action mechanism, etc. When evaluating the relationship between average exposure and response over a certain period, the area under the curve (AUC_{ss}), average concentration ($C_{avg, ss}$), maximum

concentration ($C_{max, ss}$) or trough concentration ($C_{trough, ss}$) at the steady state is often used as a measure of exposure. On the other hand, as a measure of exposure related to response that changes over time within dosage intervals, drug concentration-time profile that is matched with response measures in terms of measurement time is useful. Active metabolites are also useful for exposure measures in some instances. Moreover, as a measure of exposure, not only observed values but also values estimated using the population analysis method may be used in some instances.

2.1.5 Response measures

In addition to quantitative data such as measurement values, qualitative data such as binary data (effective or ineffective, etc.), ordered categorical data, etc. that are used in clinical studies can also be used as response measures. For response measures, observation values or endpoints characterizing efficacy or safety should be selected by taking account of the purpose of the analysis. For evaluation of the efficacy or safety of a drug, analysis using clinical endpoints or surrogate endpoints as response measures is useful. However, in early stages of the clinical development, exploratory analyses using biomarkers as response measures may also be useful for decision-making in clinical development. Furthermore, as a measure of the response for safety, the presence or absence of adverse events is occasionally used as binary data. The occurrence of adverse events can provide even more useful information if it is analyzed by classification according to seriousness, severity, whether or not they are adverse events of special interest, etc., or analyzed with use of quantitative data such as clinical laboratory test data, depending on the purpose of the analysis. In principle, missing data on response measures should be handled in the same way as efficacy analysis and safety analysis for each clinical study.

2.1.6 Factors of influences on the exposure-response relationship

Exploration of covariates as factors influencing exposure and response measures is important to better understand the exposure-response relationship and predict response more precisely based on exposure information. Investigation into covariates influencing exposure measures is often undertaken when a population pharmacokinetic model is built before exposure-response analysis. However, if there are covariates influencing both exposure measures and response measures, it is necessary to consider these covariates during exposure-response analysis, taking potential confounding into account. In general, covariates to be incorporated in the model should be determined by allowing for the magnitude of their influence, observability in the

clinical setting, etc., and it is desirable to avoid incorporating excessive covariates. Concerning points to consider when incorporating covariates into models, please refer to the relevant section of the Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis.

2.2 Methods of exposure-response evaluation

2.2.1 Initial analysis by visualization

Understanding the characteristics of data accurately before performing exposure-response analysis is a starting point for conducting the analysis adequately. Concerning evaluation of the exposure-response relationship, prior to the analysis, an exploratory graphical analysis is performed, and an overview of observed data is obtained. This provides the information for the hypothesis to be considered in the analysis. It is important to calculate summary statistics for each factor such as covariate candidates, to visualize the data by graph, and understand the shape and characteristics of distribution. Depending on the objective of the analysis, it may be sufficient to evaluate the exposure-response relationship only by graphical analysis.

2.2.2 Analysis of the exposure-response relationship (see also Appendix 6-2)

There are many different models to analyze exposure-response relationship, depending on the nature of response measures, the type of data, and the purpose of analysis. In addition to the empirical models, which are developed based on existing data, mechanism-based models are used. Often, models are linear or nonlinear where exposure measures are parameters such as AUC_{ss}, $C_{avg, ss}$, $C_{max, ss}$, and $C_{trough, ss.}$ Response measures are clinical responses related to efficacy or safety, but if there is a time lag between exposure and clinical response, time-course models of pharmacokinetics/pharmacodynamics, such as indirect response models, are also included. If it is necessary to study the long-term effect of a drug on disease that progresses over a long period of time, it may also be necessary to develop a model that takes the natural progression of the disease into consideration. In particular, when the empirical model is applied, the model should be selected based on the purpose of exposure-response analysis, and it is generally desirable to select a simpler model among those that can achieve the purpose of analysis.

In recent years, as mechanisms of pathogenesis have been clarified in various disease areas, modeling including the disposition of substances in body, such as the production and elimination of endogenous substances related to pathological conditions, has been performed. In some cases, clinical responses may be simulated more precisely by

developing a system pharmacology model. On the other hand, when mechanism-based analysis is performed, the model could become complicated and parameters that cannot be determined directly from clinical studies are sometimes required; therefore, it is recommended to use a model fit for the purpose of analysis.

2.2.2.1 Incorporation of covariates

Candidates of covariates to investigate should be chosen by taking trends of data obtained from the exploratory graphical analysis and clinical/physiological significance into account.

When the covariate is a continuous variable, linear, power, exponential, etc. models are used as regression models. In such a case, values are usually standardized with the representative values of the covariates, and used as explanatory variables.

When the covariates are discrete values, the effects of the covariates are described as additional changes or proportional changes compared to a control group in each covariate stratum.

If changes over time in covariates are important, incorporation of time-varying covariate values should be considered.

For details, please refer to the Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis.

2.2.2.2 Model diagnosis and qualification

When using a model for exposure-response analysis, it is necessary to perform model diagnosis and qualification according to the intended use. The stability and robustness of the analysis results, the validity of the parameter estimates obtained, predicting performance, etc. are evaluated referring the intended use of the model.

For details, please refer to the Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis.

2.3 Utilization of exposure-response evaluation

A correct understanding of the exposure-response relationship provides useful information for planning of an appropriate clinical study design, scientific interpretation of clinical study results, and finding optimal dosage and administration in various patient populations, thereby facilitating strategic and efficient drug development. Exposure-response models are continuously refined and updated at each phase of clinical development from the nonclinical to the post-marketing stage, so that they can contribute to efficient development planning at a subsequent stage, as well as the appropriate use of

drugs in clinical settings.

2.3.1 Utilization at the nonclinical stage

Appropriate exposure-response analysis based on results of toxicokinetics of nonclinical safety studies, nonclinical pharmacokinetic studies, and pharmacokinetic/pharmacodynamic studies in animal models of the disease to predict the clinical response can help to confirm the dependence of safety and efficacy responses on drug exposure, and may contribute to identify the most predictable measures of exposure. The selection of biomarkers to be measured in clinical studies is enabled by examining the relationship between exposure and pharmacodynamic actions, including promotion or inhibition of the production of bioactive substances, or receptor occupancy of the target, etc. that are expected from the mechanism of action. When the clinically relevant exposure is estimated, species differences such as between human and animal species in relative pharmacodynamic intensity, etc. should be considered. After the clinically relevant exposure is estimated, an informative suggestions may be obtained for dosage and administration to be studied in subsequent clinical studies when combined with methods for predicting human exposure such as physiologically based pharmacokinetic (PBPK) model or an allometric scaling.

Clinical and nonclinical information regarding preceding drugs with the same mechanism of action may be useful for exposure-response analyses. An application of quantitative systems pharmacology (QSP) modeling could also help to predict clinical responses in patients, when it is difficult to predict from responses in animal models or healthy volunteers.

2.3.2 Utilization in early phase clinical development stage

When population pharmacokinetic/pharmacodynamic analysis is performed based on data obtained early phase clinical studies, including first-in-human (FIH) studies in healthy volunteers or clinical studies in patients, the established pharmacokinetic/pharmacodynamic model could be utilized to confirm the expected mechanism of action and necessary level of exposure as well as the dosage need to achieve the targeted pharmacodynamic response. In addition, simulation of pharmacodynamic and clinical responses in the target patient population may serve as a guide to consider appropriate inclusion criteria, dosage and administration to be studied, and the necessity of dose adjustment in subsequent clinical studies. Based on the data obtained from the proof-of-concept (POC) study, in depth understanding about the relationship between exposure, pharmacodynamic, and clinical response in the target

patient population could be achieved. A highly predictable model for clinical response can be constructed by incorporations of significant covariates, the natural progression of the disease, time-course in the clinical response, and placebo effect on clinical response, etc. into the exposure-response model. Exposure-response models that are appropriately constructed based on data collected before the conduct of late phase clinical studies are useful to determine the appropriate dosage and administration, target patient population, number of patients, duration of the study, evaluation time points, etc. in the late-stage clinical study. For example, setting enrolment criteria or stratification factors for clinical studies by taking covariates that have been found to influence efficacy or safety into account should be useful for efficient drug development through providing appropriate design of late phase clinical studies.

Aside from conducting a head-to-head comparison against competing drugs with the same mechanism of action in a POC study for differentiation purpose, comparison can be possible by incorporating differences in relative intensity of pharmacodynamic response obtained from public-domain literature into the model. It is also possible to integrate literature information about the responses of competing drugs by model-based meta-analysis in order to confirm the relative position.

Analyses aimed at the evaluation of the relationship between drug concentration and changes in QT/QTc interval are mentioned in “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions & Answers (R3)” (ICH-E14 Guideline Q&A) (Administrative Notice dated May 23, 2017). For details, please refer to the ICH-E14 Guideline Q&A.

2.3.3 Utilization in late phase clinical development stage

In general, it becomes possible to establish and update a more reliable exposure-response model based on data from late phase clinical studies including dose-response and confirmatory studies, which can be applied to predict clinical responses in more diverse patient populations. Establishment of exposure-response models for efficacy and safety also make it possible to select scientifically the best dosage and administration in view of balancing the both aspects. In case of reliable prediction of clinical response can be simulated by the dose-exposure-response relationships revealed by an appropriately validated model, the simulated response derived from the model can be used as the rationale for setting the dosage and administration to be studied in confirmatory studies. For example, dosage and administration that was not directly investigated in a dose-response study can be selected as dosage and administration studied in confirmatory studies based on the model-derived prediction of responses within the range of the

investigated doses in the dose-response study. It should be noted, however, the reliability of the model-derived prediction at a dose outside the dose range of investigated in the dose-response study is generally low. Moreover, when model-derived prediction of clinical response are used for selecting the dosage in a confirmatory study, it is also desirable to model the exposure response relationship from data obtained in a well-managed controlled study involving randomization and blinding.

Furthermore, an appropriately validated exposure-response model quantitatively predicts clinical response in subpopulations stratified by significant covariates, so that it can provides a scientific rationale for the necessity to adjust the dosage and administration in the subpopulation. Similarities in dose-exposure-response relationships obtained in different ethnics or regions can suggest similarities in clinical response between the ethnics or regions. The similarity in dose-exposure-response relationships demonstrated by the model may be useful to justify study design, including the selection of dosage and administration in multi-regional clinical trials.

2.3.4 Utilization in post-marketing stage and for extending indications

In the post-marketing stage, sharing the reliable exposure-response model that was established during the course of drug development with healthcare professionals appropriately is expected to greatly contribute to the promotion of proper use of drug and personalized medicine in clinical settings. In drug development for a new formulation or an extension of indications in the post-marketing stage, the exposure-response model may presumably be applied (but are not limited) to the following purposes.

- To make it possible reliably to predict clinical response at any doses or exposure within the range of dose or exposure to be studied and thus to set the dose or exposure range to be expected no clinical relevant difference or requiring adjustment of dosage and administration.
- To predict clinical response based on the simulated exposure under the new dosage of new formulations developed for pediatric or for modified release etc. and the new dosage and administration developed in the post-marketing stage.
- To utilize for clinical study design based on the predicted clinical response in a new patient population, such as pediatrics, or other therapeutic uses by the established exposure-response model based on data from adults patients for the initial indications (It is recommended to establish the exposure-response relationship in the preceding development in adults patients if the application of the model to predict the clinical response in pediatric patients is planned to utilize for study design). The similarities

in clinical response should be demonstrated by comparing the exposure-response relationships in adult and pediatric populations.

3 Reporting and providing information

3.1 Analysis report

This section specifies points to be noted for an analysis report etc. when a model-based exposure-response analysis is performed. The analysis report should be prepared based on the analysis plan. It is desirable that the analysis report contains the particulars outlined below. However, a simplified analysis report may be appropriate in some cases, such as where the results of exposure-response analysis are included in the clinical study report, or depending on the objective of the exposure-response 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 exposure-response analysis should be presented. The objective of analysis, methods, results, and sufficient information to explain the key conclusions should be included in the summary.

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 exposure-response analysis

The objective of the exposure-response 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 exposure-response analysis

Clinical studies subject to exposure-response analysis, data used for analysis, and the overall methodology such as data analysis methods should be described. If there are any changes to the documented analysis plan, the changes and reasons should be indicated.

- Clinical studies subject to exposure-response analysis

The clinical studies subject to exposure-response analysis should be identified. For each of these studies, information about administration such as the study design and

details, target subjects and number of subjects, characteristics of subjects, investigational drugs, their dosage and administration, etc. should be summarized.

- Analytical data

Information about the endpoints related to the clinical response examined in the exposure-response analysis, time points of sample collection, time points of measurement of exposure or response measures, etc., as well as measures investigated as covariates in the exposure-response analysis should be described.

- Data analysis methods

Particulars about the 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, profile of data measured, summary statistics of demographic variables and other covariates, results of the handling of outliers and missing values, excluded data and reasons for exclusion, etc. should be presented.

- Results of model building

Descriptions should be made by clearly showing the process of reaching a decision on the final model and the rationale for the decision. The structure of the constructed exposure-response model and the parameter estimates with their standard error and, if feasible, diagnosis plots should be presented. The qualification results for the exposure-response model should also be presented.

6) Discussions and clinical applications

The validity and clinical significance of the model building and estimates should be discussed. In particular, in such cases as the dosage and administration that was not evaluated in the dose-response study is set in a confirmatory study or data are used as the rationale for dose adjustment in the package insert, it is recommended to clearly indicate

the applicable dosage range and validity of demographic data etc. based on the characteristics and range of the data used. Besides, it is also recommended to present the method for simulation based on the exposure-response model and to illustrate the results of the simulation as well as its reliability in figures.

7) Appendix

The model file describing the structure of the exposure-response model and output results, as well as the dataset used for analysis (a partial dataset from some of the subjects may be used), should be accompanied as appendix. Figures and tables not used in the main part of the report may be included in the appendix.

3.2 Regulatory submission

When the results of exposure-response analysis are used for regulatory submission, the analysis report should be provided and section 2.7, Clinical Summary, of the Common Technical Document (CTD) should be prepared based on the 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 exposure and clinical response relationships, parameter estimates obtained, the results of simulation performed based on the model, using figures and tables, and the model diagnosis and qualification results. Also, when describing the relationship between drug exposure and clinical response, information on the exposure-response analysis should be reflected appropriately in the relevant parts of the CTD, if necessary.

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

3.3 Providing information in package insert

When the results of exposure-response analysis provide useful information for appropriate use of the drug, exposure-response analysis information should be included in the “Pharmacokinetics” section of the package insert. When the simulation results are described in the package insert as the rationale for an important caution, they should be described in such a way that they can be distinguished from the actual measurement data.

Information should be provided with the prospect that exposure-response analysis results are utilized in healthcare settings, when providing information that serves as the basis for the dose adjustment policy in a specific group or is provided as the rationale for an important caution etc.

4 Relevant guidelines and documents

This guideline shows the general guidance that is scientifically plausible for conducting exposure-response analysis. While guidelines and documents that have already been notified provide descriptions regarding exposure-response analysis, this guideline integrates and organizes 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) PMSB/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) PFSB/ELD Notification No. 1023-1 October 23, 2009 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (ICH E14)
15) PSEHB/PED Notification No. 1227-5 December 27, 2017 Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11 [R1])
16) PSEHB/PED Notification No. 0118-1 January 18, 2018 Genomic Sampling and Management of Genomic Data (ICH E18)
17) PSEHB/PED Notification No. 0612-1 June 12, 2018 General Principles for Planning and Design of Multi-Regional Clinical Trials (ICH E17)

Regional guidelines and documents (pharmacokinetics)

1) PMSB/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. 0723-6 July 23, 2018 Drug-Drug Interaction Guideline for Pharmaceutical Development and Appropriate Information Provision
9) PSEHB/PED Notification No. 0515-1 May 15, 2019 Guideline on Population Pharmacokinetic and Pharmacodynamic analysis
10) PSEHB/PED Notification No. 1225-1 December 25, 2019 Revision of Guidance for Establishing Safety in First-in-Human Studies during Drug Development

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 (2003.4)
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) FDA: Guidance for Industry: Physiologically Based Pharmacokinetic Analyses — Format and Content (2018.8)
7) EMA: Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (2007.7)
8) EMA: Guideline on reporting the results of population pharmacokinetic analyses (2008.1)
9) EMA: Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (2017.2)
10) EMA: Reflection paper on the use of extrapolation in the development of medicines for pediatrics (2018.10)
11) EMA: Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (2019.7)

5 Glossary

1) Model based meta-analysis

This is an analysis method of integrating data from different studies/literature and analyzing them using a model. For data that cannot be compared directly due to differences in observation time points, patient characteristics, etc., comparisons may still be possible by adjusting for these effects using an appropriate model. However, since it is an analysis integrating data from different studies or literature, it is important to select studies or literature information that are not biased (systematic review), and the integration method, etc. is also important.

2) Quantitative system pharmacology model (QSP)

It is possible to predict the efficacy and safety of a drug by modeling the mechanism of disease onset and the mechanism of action of the drug based on detailed knowledge of the biological systems.

3) Empirical model

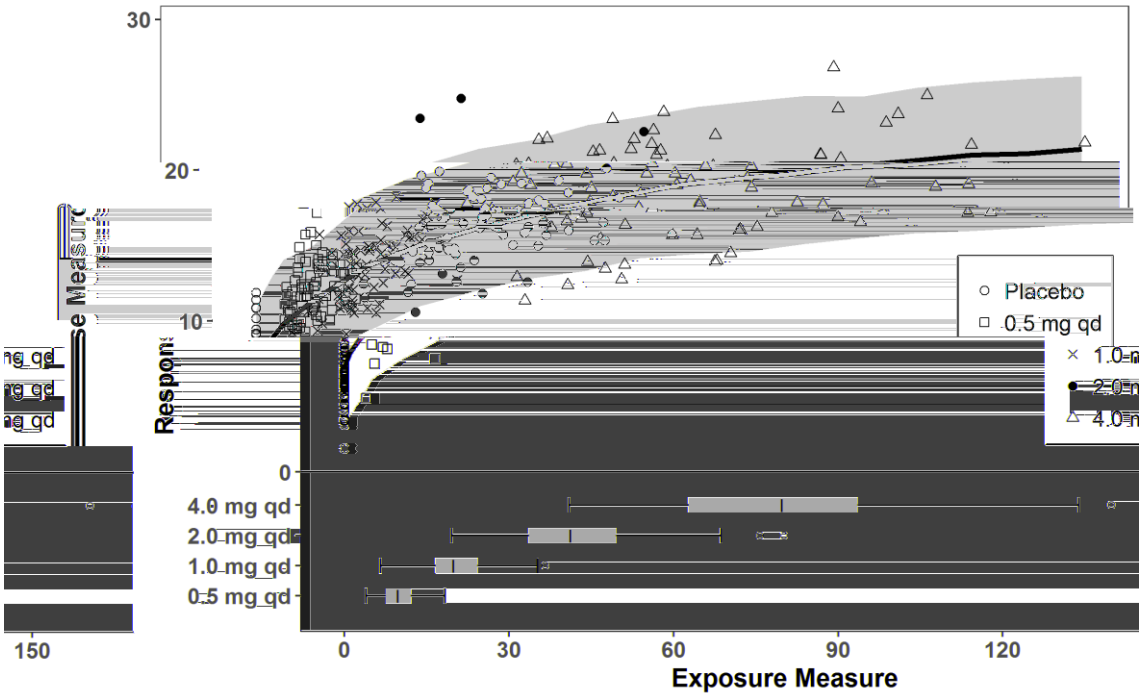
Empirical models are data-driven models in which drug concentration data and efficacy and safety data obtained from clinical studies, etc. are used. Empirical models are easy to develop, requiring fewer assumptions than mechanism-based models.

6 Appendix

This appendix shows an example of a figure generated by exposure-response analysis and examples of models related to exposure-response analysis mainly used in analyses of the pharmacometrics field (including points to consider for each model depending on the characteristics of the data used in the analysis).

6.1 Example of a figure generated by exposure-response analysis

Even if there are variations in the response at specific doses, investigation of the exposure-response data at multiple doses in a single figure may make it possible to obtain more useful information on doses at which the required response can be obtained.



The solid line and the gray area are the model-simulated median and 90% prediction interval, respectively.

Figure 2 Example of a dose-exposure-response relationship

6.2 Examples of models used in exposure-response analysis

In cases in which the response measure is a continuous value and a plateau is observed in the changes in response measure within the range of the exposure measure, the use of an E_{max} model or a sigmoidal E_{max} model (Equation 1) may be considered. If the plateau is not observed in the changes in the response measure, the use of a linear model (Equation 2) may be considered.

Equation 1. Example of the (sigmoid) E_{max} model:

$$E = E_0 + \frac{E_{max} \times Exposure^{\gamma}}{EC_{50}^{\gamma} + Exposure^{\gamma}}$$

E: Response measure
Exposure: Exposure measure
E_0: Response measure with an exposure measure of 0 (e.g., baseline or change in the placebo group)
E_{max}: Maximum effect
EC_{50}: Measure of exposure resulting in 50% of the maximum effect
γ: Hill coefficient (When γ equals 1, the model becomes an E_{max} model)

Equation 2. Example of a linear model:

$$E = E_0 + Slope \times Exposure$$

E: Response measure
Exposure: Exposure measure[1]
E_0: Response measure with an exposure measure of 0
Slope: Slope of change in response with exposure

When the response measure is binary data, the use of a logistic regression model, etc. may be considered (Equation 3).

Equation 3. Example of a logistic regression model:

[1] Logarithmically converted exposure measure can be used.

$$Logit\big(p(x)\big) = log\left[\frac{p(x)}{1-p(x)}\right] = Logit_0 + Slope_{Logit} \times Exposure$$

x: Specific value of independent variable
p(x): Probability that the response measure is x
Exposure: Exposure measure
$Logit_0$: Logit of the response measure with an exposure measure of 0
$Slope_{Logit}$: Slope of change in logit with exposure

In the following cases, analysis of time-course data should be considered.

- When the inter-occasion variability in the response measure is large
- When the exposure-response relationship at the primary evaluation time point appears inconsistent with other evaluation time points
- In situation with frequent or informative dropouts on the response are observed.
- When the time-courses of the response measure are important, etc.

In these cases, analysis should be performed by using the exposure and response measures obtained over time, and a term of time should be incorporated into the model. For example, when it takes time to reach the maximum effect, the E_{max} model with time-dependent onset of the maximum effect may be considered, as shown in Equation 4. Similarly, when the longitudinal binary or ordered categorical data is modeled, a model that incorporates a term of time is considered.

Equation 4. Example of the E_{max} model with time-dependent onset of the maximum effect:

$$E_i = E_{0,i} + \frac{E_{max} \times Exposure}{EC_{50} + Exposure} \times \left(1 - e^{-ktr \times Time_i}\right)$$

E_i: Response measure at time point i
$Time_i$: Time at time point i
Exposure: Exposure measure
$E_{0,i}$: Response measure without exposure at time point i
E_{max}: Maximum effect
ktr: Rate constant for the onset of effect
EC_{50}: Measure of exposure resulting in 50% of the maximum effect

If response variables in the placebo group change over time, a placebo model as shown in Equation 5 may be considered.

Equation 5. Example of a placebo model:

$$E_{placebo,i} = E_{max,placebo} \times \left(1 - e^{-k_{placebo} \times Time_i}\right)$$

$E_{placebo,i}$: Response measure of the placebo group at time point i
$Time_i$: Time at time point i
$E_{max,placebo}$: Maximum placebo effect
$k_{placebo}$: Rate constant for the onset of the placebo effect

Disease progression models are used to examine the long-term effects of a drug on a disease that progresses over a long period of time. In disease progression models, clinical symptoms in patients on drug treatment can be expressed as a composite of disease progression and the effect of the drug. Although the example of Equation 6 represents the symptomatic effect of a drug, the effect of a drug on disease progression may be investigated by examining the impact on the slope of the disease progression over time.

Equation 6. Example of a disease progression model:

$$E_i = E_0 + \alpha \times Time_i + Slope \times Exposure$$

E_i: Response measure at time point i
E_0: Response measure with an exposure measure of 0
α: Slope of disease progression over time
$Time_i$: Time at time point i
Slope: Slope of change in response with exposure
Exposure: Exposure measure

Survival analyses may be used to analyze the time-to-event data. A proportional hazard model etc. may be used where the probability that an event may occur at a certain moment, i.e., so-called hazard, is used to build a model and an exposure measure is incorporated as an explanatory variable for the hazard (Equation 7).

Equation 7. Example of proportional hazard model：

$$h(t) = h_0(t) \times exp(\beta \times Exposure + \beta_1 \times Cov_1 + \cdots + \beta_n \times Cov_n)$$

$h(t)$：hazard at time point t

$h_0(t)$：baseline hazard

β：Slope of change in hazard with exposure

Exposure：Exposure measure

β_1、β_n：Slope of change in hazard with covariate

Cov_1、Cov_n：covariate