Clinical Pharmacokinetic Studies of Pharmaceuticals

This document is an informal translation of the official text that was promulgated in Japanese on 1 June 2001 by Ministry of Health, Labour, and Welfare and is intended for use as a reference in conducting clinical pharmacokinetic studies of pharmaceuticals.

1. Introduction

This document describes the scope and basic principles of clinical pharmacokinetic studies necessary for the submission of a new drug application (NDA) and for re-examination of approved drugs. It is aimed at obtaining human pharmacokinetic information necessary for new drug development and for ensuring the appropriate use of medicines.

Clinical pharmacokinetic studies are performed to examine the absorption, distribution, metabolism, and excretion of a drug under investigation (investigational drug and approved drug) in healthy volunteers and/or patients. Data obtained from such studies are useful for the design and conduct of subsequent clinical trials. They are also necessary for appropriate analysis and evaluation of the efficacy and safety data obtained in clinical trials for new drug development and in post-marketing clinical trials. The results of non-clinical pharmacological and toxicological studies should be evaluated in conjunction with the results from non-clinical and clinical pharmacokinetic studies to provide useful information for the appropriate and safe conduct of clinical trials and for the evaluation of the mechanism of action in human subjects.

Outcomes of clinical pharmacokinetic studies are useful for determining the appropriate use of medicines according to patient characteristics, such as disease and genotype of drug-metabolizing enzymes, and for predicting the influence of pharmacokinetic drug interactions. The results can also provide information for therapeutic drug monitoring (TDM). It is important to evaluate pharmacokinetic parameters of individual subjects (patients or healthy volunteers) in close association with drug efficacy and adverse drug reactions observed in each subject.

Physical and chemical properties, pharmacological actions, pharmacokinetics, toxicity, and use in clinical practice will differ between any two investigational drugs. It is necessary, therefore, to implement the most appropriate development plan for each investigational drug. Thus, this document may not uniformly be applicable to every investigational drug. For investigational drugs prepared using gene technology, the International Conference on Harmonization (ICH) guideline “Non-clinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (2000)” indicates the basic principles that are to be followed.

When conducting clinical pharmacokinetic studies, appropriate methods should be chosen according to the inherent properties of the investigational drug and be based on the principles stated below, while at the same time taking full advantage of existing information from both non-clinical and clinical studies. Additional studies may be necessary. As a result, more efficient development of a new medicine may be achieved, thereby avoiding unnecessary studies.

1.1 Scope of the Document

The scope of this document includes the series of clinical pharmacokinetic studies that should be conducted primarily for the purpose of drug development; most can be included within the category "Human Pharmacology" of "General Considerations for Clinical Trials (1998)." In other words, this document is applicable to clinical pharmacokinetic studies conducted throughout clinical phase I, phase II (early and late), and phase III studies.

However, in the case of a pharmacokinetic study that was not completed before NDA

submission due to special circumstances, or when additional concerns are recognized after a drug is marketed, a pharmacokinetic study is sometimes conducted after NDA submission or after marketing. In such cases, this document should also be useful.

1.2 Relationships with Other Guidelines

This document outlines the basic principles for clinical pharmacokinetic studies. Although previously published guidelines include descriptions of clinical pharmacokinetic studies, there are differences in their scope and content. The present document integrates their contents related to pharmacokinetics and supplements the pharmacokinetic data with new findings. Therefore, it should be used as a reference for the design and conduct of clinical pharmacokinetic studies.

2. Analytical Methods

Assays to measure the concentration of an investigational drug or its metabolites in human tissue samples should be validated in terms of accuracy, precision, specificity, and quantitation limit. For validation, it is necessary to consider the stability of samples during the time from collection through transportation, storage, and analysis. Assays should be conducted according to the principles of "Good Laboratory Practice."

Use of an identical assay method throughout drug development, from the early stage until clinical trials, is desirable, but the method may differ among studies, or a new method may be adopted during development. In such cases, it is necessary to perform validation in order to clarify the relationship among assays (cross-validation).

When an investigational drug originates from an endogenous substance or when interference with endogenous substances is anticipated, comparison of the data with data from a placebo group or with samples obtained before administration of the test substance may be necessary.

If the concentration of an investigational drug and/or its metabolites in biological materials cannot be detected/measured despite efforts to improve the sensitivity of the assay, an explanation should be given. Determination of pharmacokinetics in organs/tissues cannot usually be performed in human subjects but may be estimated from pharmacologic or adverse effects whenever necessary.

3. Investigational Drug/Product

During the early stages of development, pharmacokinetic parameters are generally not determined using a final formulation. However, pharmacokinetic studies using the final formulation need to be conducted prior to submission of the NDA.

When a stable isotope- or radioisotope-labeled investigational drug is used, care should be taken that the labeling does not change the pharmacokinetic properties of the drug.

4. Compliance with Good Clinical Practice

Clinical pharmacokinetic studies should be conducted in compliance with the Ministry of

Health and Welfare (MHW) Ordinance No. 28 "Good Clinical Practice (1997)" in order to ensure the safety of subjects, the protection of human rights, the maintenance of scientific quality, and the reliability of results.

5. Required Clinical Pharmacokinetic Data " Note # $

Information on the absorption, distribution, metabolism, and excretion of an investigational drug should be obtained from healthy people and patients. The pharmacokinetic parameters listed in Section 7.1. “Pharmacokinetic Analytical Methods” are calculated from these results.

Studies should be appropriately designed to obtain the correct information. When conducting studies, due consideration should be given to individual variation, and an appropriate number of volunteers should be used. The influence of frequent blood collection on the volunteers should also be considered.

In light of the expected clinical usage and properties of an investigational drug, populations that may show pharmacokinetic profiles different from standard healthy volunteers, such as the elderly and children, patients with hepatic or renal disorders, or subjects with decreased activity of drug-metabolizing enzymes due to genetic polymorphisms, must also be investigated.

After considering drug properties and subject safety, pharmacokinetic parameters should be obtained after intravenous administration, even for drugs that are not used intravenously in the clinical setting, if necessary and if possible.

When clinically significant drug interactions are suspected from the results of non-clinical studies, appropriate clinical drug interaction studies should be conducted after ensuring the safety of the volunteers.

5.1. Absorption

An absorption study should be conducted using the route of administration that will be used clinically. Information on changes in blood levels (concentration in whole blood, plasma, or serum) of the drug substances is necessary, regardless of the route of administration.

For investigational drugs that show efficacy via the systemic circulation, pharmacokinetic parameters such as the absorption ratio, bioavailability, and absorption rate should be estimated. In cases of oral administration, comparison with results from intravenous administration is useful in order to estimate the absorption ratio and bioavailability, and to clarify the extent of first-pass effects.

As absorption from the gastrointestinal tract is likely to be affected by meals, the effects of a meal on gastrointestinal absorption should be evaluated for investigational drugs that are administered orally. In such cases, a final formulation must be used.

In the case of investigational drugs that are intended to be used locally, absorption from the application sites should be investigated using a final formulation.

5.2. Distribution

The volume of distribution should be calculated on the basis of drug concentration changes in the circulation of human subjects. Plasma protein binding (unbound fraction of a drug) and

partition ratio to blood cells must also be determined. When the unbound fraction of a drug is low, the nature of its binding protein(s) should be clarified.

It is useful to estimate the distribution in human organs/tissues in general from information from non-clinical pharmacokinetic study results. In special cases, direct measurement of drug concentrations in tissues may be necessary in clinical studies.

5.3. Metabolism

The pathway and ratio of metabolism should be assessed by measuring an investigational drug and its metabolites in blood, urine, and, if necessary, feces. Major enzymes and those subtypes responsible for the metabolism of the drug should be determined from the results of non-clinical studies using mostly human tissue-derived materials and genetically expressed human drug-metabolizing enzymes.

If total clearance is largely due to metabolic clearance, and a drug is expected to be administered repeatedly in clinical practice, investigation of a change in metabolic pattern via induction or inhibition of drug-metabolizing enzymes with repeated dosing is recommended.

If active metabolites that contribute significantly to the efficacy and/or adverse reactions, the blood-concentration time course of the active metabolites should be evaluated. Some drug-metabolizing enzymes exhibit genetic polymorphisms, resulting in large decreases in activity. When these enzymes are involved in the major route of metabolism of an investigational drug and an evaluation of its metabolism in clinical studies is possible, it is important to assess to what extent pharmacokinetic parameters are influenced by the genetic polymorphism.

Characteristics and degree of metabolism in the small intestine should be taken into consideration whenever an investigational drug is administered orally and metabolized by the P450 isoforms (e.g., CYP3A4) that are found in the small intestine in significant amounts.

5.4. Excretion

Information on the urinary excretion (rate and extent) of an investigational drug and its metabolites should be obtained. Fecal excretion should also be determined whenever necessary. Whether the excretion of an investigational drug is dependent on hepatic clearance or renal clearance should be determined considering total clearance.

When evaluating fecal excretion, consideration should be also given to the possibility that unabsorbed drug may appear in the feces.

6. Study Methods

6.1. Subjects

6.1.1. Studies at the Early Stages of Drug Development

Studies should be conducted under well-controlled conditions usually with an appropriate number of healthy volunteers, in order to determine the pharmacokinetics of a drug. If investigation of a drug poses a significant risk to healthy volunteers, the studies should be conducted in patients with the target disease.

When a single administration of a drug is oral, the drug should, in principle, be administered

after more than 10 hours of fasting.

The linearity of pharmacokinetics, route of clearance, and influence of meals should be examined at this early stage of drug development.

In cases where repeated doses are to be given, the drug should be given according to the standard clinical dosing regimen.

The influence of weight, age, gender, genetic factors, and drinking and smoking habits should also be investigated whenever necessary.

If significant individual differences in pharmacokinetics due to genetic polymorphisms are expected, it is desirable to conduct a study including or excluding subjects who have specific genotypes, based upon discrete criteria such as genetic screening.

6.1.2. Studies with Patients at the Late Stages of Drug Development

Patients who have a target disease are investigated to determine pharmacokinetic profiles, while taking into consideration any relevant background factors. It is desirable to investigate relationships between dosage and drug concentrations in the blood, and between drug concentrations in the blood and therapeutic effects.

If the results indicate that the pharmacokinetic profiles of patients differ from those of healthy volunteers, it is necessary to identify possible reasons and to consider conducting a pharmacokinetic study with an appropriate number of patients to confirm the difference.

Conducting an additional study with healthy volunteers may be necessary if, during phase II or III, changes, such as higher doses for which safety has not been confirmed, altered formulations, or different crystal forms, must be made to the development plan.

6.1.3. Studies after New Drug Application and Approval

Sometimes sufficient information regarding influences on pharmacokinetic profiles of intrinsic and extrinsic factors such as age, gender, body weight, genetic factors, severity of disease, complications, meals, drinking and smoking habits, concomitant drugs, or other factors cannot be obtained prior to submission of the NDA. In such cases, a study with healthy persons or patients may be required after the drug has been submitted for NDA approval or after the drug has been marketed.

6.2. Types of Study

There are two ways to evaluate the clinical pharmacokinetics of a drug. One method is a conventional "standard pharmacokinetic study," and the other is a "population pharmacokinetic study." The primary objective of the former method is to evaluate the pharmacokinetic profile of the investigational drug by single-dose or repeated-dose study, under strictly managed conditions, following a defined protocol. The latter method evaluates pharmacokinetic profiles by utilizing the blood concentration data obtained from a clinical study with the primary objective of determining the efficacy and safety of a drug. A decision to adopt either of the methods should be based on the objectives of the study and the stage of development. Usually, the pharmacokinetic characteristics of a drug are examined by the "standard pharmacokinetic study."

6.2.1. Standard Pharmacokinetic Study

A standard pharmacokinetic study is the conventional method for evaluating the pharmacokinetics of a drug in human subjects. In such a study, subjects are given a single dose or repeated doses of an investigational drug. Then, blood and urine samples are collected in compliance with a fixed schedule. Fecal samples may also be necessary. Then, the concentration of the investigational drug and its metabolites is measured in these samples and the pharmacokinetic profile of the investigational drug is evaluated.

Based upon the preceding information, the rate of absorption and elimination should be estimated, and the results should be utilized for the determination of optimal points for sample collection.

6.2.1.1. Single-dose Study

In a single-dose study, the concentration of an investigational drug and its metabolites are measured in blood following a single administration to healthy volunteers and/or patients. Furthermore, the amount and composition of the investigational drug and its metabolites in blood, urine, and, when necessary, feces are measured to evaluate mass balance. Plasma protein binding (identity of binding proteins and the unbound ratio), bioavailability, linearity of pharmacokinetics, and the effects of meals should also be investigated in the single-dose study.

The initial dose should be determined by referring to data from toxicity studies, toxicokinetic and non-clinical pharmacokinetic studies, as well as to results from previously conducted metabolic studies with human tissues, properties of pharmacologic actions, and, if available, clinical studies conducted abroad.

Usually, a small number of healthy subjects are recruited for the study, and the dosage is increased in a stepwise fashion, starting with the lowest dose, while monitoring any occurrence of adverse events.

In order to evaluate the relationship between dosage and pharmacokinetic parameters, several doses should be used, including the estimated clinical dose and a dose higher than the estimated highest clinical dose.

In a study involving patients, evaluating not only the relationship between dosage and blood concentrations, but also that between blood concentrations and pharmacologic effects may provide valuable information.

An appropriate number of subjects should be used to determine the inter-individual variability of drug effects.

A sufficient number of samples should be obtained at appropriate time points to estimate blood concentrations of the drug. However, consideration should be given to ethical and medical concerns regarding excessive blood collection. The "Guideline for Bioequivalence Study (1997)" is a useful reference. Urine samples should be collected until the unchanged drug and its metabolites are no longer detectable. When fecal excretion plays a significant role in the pharmacokinetics of a given drug, the amount should also be studied.

6.2.1.2. Repeated-dose Study

Changes in pharmacokinetic parameters, confirmation of steady state concentrations, and the potential for accumulation should be evaluated when a drug is given repeatedly, according to the dosing route and schedule planned for clinical practice (Note 2, Note 3). The results should be compared with changes in blood concentrations estimated from the single-dose study results. The degree of changes in pharmacokinetic parameters depending on the administered dose and frequency of dosing should be evaluated with respect to the dose and the dosing regimen intended for clinical use.

The appropriate number of subjects should be determined based on the results of single-dose studies.

The frequency of sampling after first administration should be that enabling the evaluation of pharmacokinetic profiles in subjects. At the time of midterm administration, sampling should be performed at a few points corresponding to trough concentrations (C_{trough}) or peak concentrations (C_{peak}). At the time of final administration or steady state, a sufficient number of sampling time points should be taken to evaluate the elimination rate, accumulation, and linearity. However, consideration for the stress on the volunteers is necessary.

6.2.2. Population Pharmacokinetic Approach (Note 4)

With a population pharmacokinetic approach, usually a large number of subjects participate in the study, while the number of samples collected from each subject can be small. The advantages of this approach include less inconvenience and stress on the subjects involved. This approach is considered suitable for special populations such as the elderly and children.

Population pharmacokinetic study designs often include pharmacokinetic screening methods such as the single-trough screen, multiple-trough screen, and full screen. The choice of methods is based on the dosage form, feasibility, and whether the outcome of the study conforms to the study objectives.

Representative values of pharmacokinetic parameters of population (e.g., mean), factors that affect pharmacokinetics, the degree of the effects, and inter- and intra-individual variability can be obtained from a population analysis that is appropriately planned and implemented. Compared with the huge number of patients, in whom the medicine will be used after approval, the number of subjects in the study population is limited. Thus, to maximize the information obtained from the population pharmacokinetic approach, study procedures including the timing and number of samplings, methods for handling specimens, and data analysis methods must be appropriately planned. The sample size should be appropriate and sufficient for the study objectives, population characteristics, dosage forms, and feasibility. It is important to record the time of administration and sample collection accurately. Simultaneous measurement of drug concentrations in the blood with efficacy and safety endpoints is useful for understanding drug concentration/response relationships. Furthermore, population pharmacokinetic parameters can be utilized with the Bayesian estimation method, which estimates pharmacokinetic parameters of individual subjects from a small amount of blood concentration data.

6.3. Pharmacokinetics/Pharmacodynamics Study (PK/PD Study)

A PK/PD study in which pharmacological response levels and drug concentrations are analyzed will be useful for clarifying the dose-response relationship and relationships among dosage regimens, drug concentrations, efficacy, and adverse effects. In conducting the PK/PD study, drug concentrations and clinical endpoints (true or surrogate endpoints, or pharmacological endpoints that were validated for relation to clinical effects or adverse effects) are measured in subjects for the evaluation of efficacy and safety. In some cases, comparison with a placebo group may be useful. It is necessary to consider the relationship between surrogate endpoints and true clinical endpoints.

A PK/PD study of an investigational drug is particularly important when there is no parallel relationship between the concentration of the drug in the blood and efficacy. These include cases where the efficacy of a drug is achieved by its presence at the sites of action (receptor, etc) after its elimination from blood or when the onset of efficacy is seen long after its binding to target sites.

6.4. Pharmacokinetic Study needed for Extrapolating Foreign Data to Japanese

Data from clinical pharmacokinetic studies are essential for the complete clinical data package. Study subjects should be Japanese individuals who live in Japan, but Japanese individuals who live overseas may also be used if their pharmacokinetic characteristics are generally accepted to be the same as those who live in Japan. Pharmacokinetic characteristics are primarily determined by intrinsic factors, but can also be extrinsically influenced; thus, it is necessary to consider possible environmental factors, such as diet, in order to obtain data by which pharmacokinetic profiles of Japanese individuals who live in Japan can be estimated. The scope of any pharmacokinetic study involving Japanese individuals who live in Japan or abroad should be determined for each drug while considering its physical and chemical properties, previous pharmacokinetic data, and intended clinical use. In order to extrapolate from foreign data, it is necessary to compare the data on ethnically diverse populations with the data on Japanese populations living in Japan or living overseas (where such data are obtained from a pharmacokinetic study of adequate size), with due consideration to comparability in all aspects, including study design, study protocol and analytical methods.

7. Analytical Methods

Data should be analyzed from both a pharmacokinetic and statistical point of view. It is also useful to analyze results both with and without the use of pharmacokinetic models. Appropriateness of the statistical analysis should be secured by the “Principle of Statistical Analysis of Clinical Test (1998).” At least major methods for clinical pharmacokinetic data analysis should be stated in the study protocol. Details of the procedure can be mentioned in the protocol for data analysis.

7.1. Pharmacokinetic Analytical Methods

In a standard pharmacokinetic study, a sufficient number of data collection points should be included, and pharmacokinetic parameters, such as area under the blood concentration-time curve (AUC), clearance, maximum blood concentration (C_{max}), minimum blood concentration (C_{min}), time to reach maximum blood concentration (t_{max}), volume of distribution at steady state (Vd_{ss}), mean residence time (MRT), and half life ($t_{1/2}$), should be determined by using model-independent analytical methods. In addition to the above parameters, the rate constant and information about the volume of distribution (V_1, $Vd_{\%}$, and Vd_{ss}) can be obtained using pharmacokinetic models like a compartment model. Models that can describe drug concentrations in a blood-versus-time profile are useful to estimate changes in blood concentrations caused by differences in dosage and dose regimen, and may be used to tailor individual dosing plans. The analysis should also be extended to include a PK/PD analysis.

7.2. Statistical Analytical Methods

It may be preferable to illustrate concentration-versus-time profiles with a graph. Based on an analysis of individual data, variations of drug concentrations and pharmacokinetic parameters should be summarized appropriately. In a study with a sufficient amount of data, mean values, variance (between- and within-subjects, if possible), and confidence intervals of drug concentrations and pharmacokinetic parameters should be estimated using appropriate statistical methods that are determined in advance while considering the study design. Major variables such as drug concentrations and pharmacokinetic parameters should be analyzed based on their statistical properties of distribution, and data transformation such as logarithmic transformation should be performed whenever necessary. Pharmacokinetic models on which data analyses are based, estimation methods for pharmacokinetic parameters, software used for analysis (package), and handling of outliers and data points lower than the limit of quantitation must be clearly stated.

8. Evaluation and Reporting of Pharmacokinetic Information

8.1. Evaluation of Analytical Results

In order to support clinical effects with the results of a clinical pharmacokinetic study, it is necessary to confirm or estimate that the investigational drug or its metabolites are present at an active site at an appropriate concentration for an appropriate time. Additionally, the concentration at which pharmacological effects appeared in primary and secondary pharmacologic studies and in safety pharmacological studies, and the relationship between toxicity and toxicokinetic data must be compared with clinical pharmacokinetic data in order to examine any relationship with clinical effects and adverse drug reactions.

If the pharmacokinetics show non-linearity due to the dose and/or administration period, potential mechanisms should be discussed. If a difference is found between the results of simulation by using a pharmacokinetic model and the actual data, the underlying cause of the difference should be discussed.

The administration schedule in subsequent clinical studies in patients should be designed in consideration of drug clearance and volume of distribution obtained from clinical

pharmacokinetic studies in the early stages of development. The validity of the dosing schedule in previously conducted clinical studies and the results must be confirmed. The pharmacokinetic characteristics of the investigational drug in patients should be clarified by comparing them with those of medicines within the same therapeutic category.

In cases of possible gender differences or genetic polymorphisms in the pharmacokinetics of a drug, it is necessary to discuss whether the dosage and dose regimen should be modified according to these factors. In comparison with non-clinical pharmacokinetic study results, the possibility of drug interactions and the clinical significance of these interactions must be discussed. The package insert should include such information either under "Cautions in Concomitant Use" or "Contraindications".

For extrapolation of clinical data from other countries, ethnic differences in pharmacokinetics must be discussed.

8.2. Reporting Analytical Results and Providing Information

Results of clinical pharmacokinetic studies should be filed as reports. To establish a standard administration method based on scientific rationale and dose adjustment for special populations, it is necessary to provide appropriate information with supporting data in the package insert and elsewhere.

9. Post-marketing Survey

Information obtained during the drug development stage is not necessarily sufficient for drug evaluation, given that it is collected from a limited number of people. Thus, collection of post-marketing information is important. Even for a drug that may causes serious problems in patients whose drug disposition activities are deviated from the average, there may be a case where sufficient information was not obtained before marketing approval. In this case, information on the changes in drug disposition should be continuously explored after marketing by TDM or some other means.

10. Glossary

Bayesian estimation & Method of obtaining pharmacokinetic parameters by applying the Bayesian theorem. Pharmacokinetic parameters are estimated for each patient based on population parameters already obtained and the blood concentration data for each patient. This method is useful for analyzing the pharmacokinetic characteristics of patients, given that it enables an estimation of individual pharmacokinetic parameters and the blood concentration - time relationship from limited data. The method has been used in the area of therapeutic drug monitoring for establishing dose and schedule in each individual.

Clearance (CL) & Rate of drug disappearance from the body indicated as a volume of body fluid (usually blood) cleared per unit time.

CL =(Rate of disappearance) / (drug concentration)

The contributions of the liver, kidney, and metabolism to total clearance are called hepatic

clearance, renal clearance, and metabolic clearance, respectively.

F & Fraction of an orally administered compound that enter the systemic circulation.

Fecal excretion ratio & Ratio of the amount of drug and its metabolites excreted in feces to the administered dose

' ( ) " Good Clinical Practice $& Criteria to ensure the validity of clinical testing of a drug.

GLP (Good Laboratory Practice) & Criteria to ensure the reliability of non-clinical safety studies of a drug.

Half-life & Time needed for the blood or plasma concentration of a drug to decrease by half.

* (+ & International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH was organized by both regulatory agencies that are responsible for new drug approval and pharmaceutical manufacturing associations of the European Union, Japan, and the United States to promote the international harmonization of documents for NDA.

Linearity & When the rate (e.g., absorption rate, metabolic rate) changes in proportion to the administered dose, the relation between them is linear. In a general sense, the pharmacokinetic characteristics of a drug are considered to be linear when every pharmacokinetic parameter related to rate indicates linearity. In this situation, blood concentration, AUC, and C_{max} change in proportion to the administered dose. That is, regression lines for these relationships should pass through the origin of the coordinate axes. Pharmacokinetic parameters related to the rate (e.g., clearance, half-life, MRT) are constant regardless of dose.

) , " Pharmacodynamics $& Studies on the relationships (including temporal relationships) between drug concentration around the organ/tissue and pharmacological effects that are induced by the modification of biological functions.

) - " Pharmacokinetics $& Studies on the absorption, distribution, metabolism, and excretion of drugs and studies on the enzymes, transporters, etc. involved in these processes. In the case of human studies, the profile of a drug and its metabolites in blood; their half-lives and rates of elimination, for example, are studied.

Population pharmacokinetic study & Approach used to obtain pharmacokinetic characteristics of a

patient population and its sub-populations by multivariate analysis of various elements that constitute background components of test subjects, as explanatory variables of pharmacokinetic parameters. The analysis is based on a non-linear mixed-effect model that depends on mathematical analyses of estimates of representative values of the population and each element as explanatory variables.

Single-trough screen & Method used to estimate the steady-state level of a drug after repetitive administration by collecting one specimen from each subject immediately prior to the next administration (trough concentration). It is possible to obtain information on the distribution of the drug concentration in blood after administration of a specific dose, when there are many subjects, given that variation caused by sampling and analyses is small, and intra-individual variation is small. With due consideration for these findings, together with information on the distribution of data on therapeutic effects and adverse events, it may be possible to estimate the therapeutic effective blood level. Compliance is a prerequisite for this analysis. Therefore, it is necessary to confirm at least two instances of repetitive drug intake before blood sampling. The number of confirmations depends on the half-life of the drug. This one-point analysis should be applied only to trough concentration measurements and not to peak concentration measurements, except for cases of intravenous drug administration. This method is easy to carry out; however, there are limitations to the analyses, and the variation obtained tends to be large. Therefore, this method is not recommended for population pharmacokinetic studies. This method should be restricted to cases where other types of studies cannot be conducted.

Multiple-trough screen & Method used to estimate the steady-state level of a drug after repetitive administration by collecting several specimens (more than two) from each subject. In addition to the information obtained by the single-trough screen, it is also possible to confirm the reproducibility of blood concentrations among individuals and to help increase the reliability of measurements. It is possible to assess both inter-individual and intra-individual variation, together with the total variation in blood levels. It is also possible to analyze the data by associating them with the background information on patients. With due consideration to these findings, together with the information on therapeutic effects and adverse events, it may be possible to estimate the therapeutically effective blood level. Pharmacokinetic data obtained from multiple-trough screening are clearance data. Variations between individuals are analyzed by a non-linear mixed effects model. This method requires data from many patients. Therefore, it is necessary to take blood samples from all or most of the patients participating in the clinical study. It is also necessary to confirm patient compliance.

Full screen (Full population PK sampling design, Full pharmacokinetic screen) & Method in which blood samples are collected several times (usually 2-6 times) from each patient

at unspecified time points after drug administration. It is possible to include data from blood sampled only once from each patient. Analysis of blood from many patients at different time points yields information on the pharmacokinetic characteristics of the population receiving the test substances. It is possible to obtain many pharmacokinetic parameters by analysing the data with non-linear mixed effect model, including clearance, to evaluate inter- and intra-individual variation, and to associate the variation with background information on patients to identify the cause of individual differences. This method is suitable for assessing the pharmacokinetics of a drug in a patient population and also for conducting PK/PD studies. This method also requires blood samples from all or most of the participating patients. It is also necessary to confirm patient compliance and to record the exact time of drug intake and blood sampling.

Renal excretion ratio & Ratio of unchanged drug excreted in the urine to the administered dose. There is also a case in which the term refers to the sum of unchanged drug and its metabolites excreted into urine. The terms should not be used interchangeably.

Standard pharmacokinetic study & Conventional pharmacokinetic study where collection of specimens from the same individuals is repeated many times. Pharmacokinetic parameters in each individual can be obtained by this method.

Therapeutic drug monitoring (TDM) & Monitoring the concentration of a drug or its active metabolites in biological samples, usually blood, from patients for the purpose of (1) establishing an appropriate dose, (2) promoting therapeutic results by comparing the blood level of a drug with its efficacy or side effects, and (3) monitoring t patient compliance.

Volume of distribution (Vd) & Apparent volume in which the drug is distributed throughout the body.

Vd = (amount of drug in the body) / (blood concentration)

V_1, $Vd_{\%}$, and Vdss indicate the volume of distribution of the central compartment, Vd calculated from % phase of elimination, and Vd from steady state, respectively.

11. Related Guidelines and Guidances

11.1. ICH Guidelines Related to Pharmacokinetic Studies

. / & Structure and Content of Clinical Study Reports (1995)
. 0 & Dose-response Information to Support Drug Registration (1994)
. 1 & Ethnic Factors in the Acceptability of Foreign Clinical Data (1998)
. 2 & Guideline for Good Clinical Practice (1996)
. 3 & Studies in Support of Special Populations: Geriatrics (1993)
. 4 & General Considerations for Clinical Trials (1997)
. 5 & General Considerations for Clinical Trials (1998)

. 10 & Guidelines for Selection of Control Groups in Clinical Studies (draft) (1999)
. 11 & Guidelines for Clinical Studies of Medicines in the Pediatric Population (2000)
6 / & Timing of Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (1999)
S3A & Note for Guidance on Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Studies) (1998)

11.2.Japanese Guidelines

Guideline for the Development of Drugs for Pediatrics (1982)
Guideline for the Design and Evaluation of Slow-releasing Preparations (oral preparation) (1988)
General Guideline for the Clinical Evaluation of New Drugs (1992)
Guideline for the Bioequivalence Study for Generic Drugs (1997)
Guideline for Non-clinical Pharmacokinetic Studies (1998)
Guidance for the Bioequivalence Test for Changing Oral Solid Formulation (2000)
Guidance for the Bioequivalence Test for the Oral Solid Preparation Containing Different Doses (2000)

Guidelines for specific disease

Guideline for the Clinical Evaluation of Anti-Arrhythmic Drugs (1984)
Guideline for the Clinical Evaluation of Anti-Angina Pectoris Drugs (1985)
Guideline for the Clinical Evaluation of Analgesics (1985)
Guideline for the Clinical Evaluation of Oral Contraceptives (1987)
Guideline for the Clinical Evaluation of Drugs for Cerebral Circulation/ Metabolism (1987)
Guideline for the Clinical Evaluation of Anti-lipidemics (1988)
Guideline for the Clinical Evaluation of Drugs for Anxiety (1988)
Guideline for the Clinical Evaluation of Anesthetics (1988)
Guideline for the Clinical Evaluation of Cardiac Drugs (1988)
Guideline for the Clinical Evaluation of Anti-hypertensives (1989)
Guideline for the Clinical Evaluation of Anti-cancer drugs (1991)
Guideline for the Clinical Evaluation of Anti-dementia drugs (draft), 1998)
Guideline for the Clinical Evaluation of Antibiotics (1998)
Guideline for the Clinical Evaluation of Drugs for Impairment of Cerebral Blood Vessels (2001)
Guideline for the Evaluation of Anti-cancer Drugs by Phase I Clinical Trial Results (draft) (1998)
Guideline for the Clinical Evaluation of Drugs for Osteoporosis (1999)

11.3. Guidances Abroad

11.3.1 FDA Guidances

Guidance for Industry, Studies in Support of Special Populations: Geriatrics (1994)

Guidance for Industry, Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well-characterized, Therapeutic, Biotechnology-derived Products (1995)

Guidance for Industry, Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in vitro (1997)

Guidance for Industry, In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches (1997)

Guidance for Industry, Food-effect Bioavailability and Bioequivalence Studies (1997)

Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (1998)

Guidance for Industry, General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (1998)

Guidance for Industry, In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling (1999)

Statistical Procedures for Bioequivalence Studies using Standard, Two-treatment Crossover Design (Issued 1992, Posted 1998)

Bioanalytical Methods Validation for Human Studies. Draft guidance (1999)

BA and BE Studies for Orally Administered Drug Products. General Considerations. Draft guidance (Issued 1999, Posted 1999)

Average, Population, and Individual Approaches to Establishing Bioequivalence. Draft guidance (Issued 1999, Posted 1999)

Guidance for Industry, Population Pharmacokinetics (1999)

11.3.2. EU Guidances

Note for Guidance on the Investigation of Drug Interactions (1997)

Pharmacokinetic Studies in Man (1987)

12. Notes

Note 1:

Blood drug concentrations (plasma concentration, serum concentration, and whole blood concentration) that are observed in terms of the total process of absorption, distribution, metabolism, and excretion are important to determine the pharmacokinetic profiles of the medicine. Blood concentration-area under the curve versus time (AUC), volume of distribution (Vd, Vd/F), clearance (CL, CL/F), elimination half-life ($t_{1/2}$), mean residence time (MRT), time to reach maximum blood concentration (t_{max}), mean blood concentration (C_{av}), maximum concentration (C_{max}) or peak concentration (C_{peak}), and minimum concentration (C_{min}) or trough concentrations (C_{trough}) are useful parameters in pharmacokinetics. If AUC, C_{av}, C_{max}, and C_{min} are proportional to dose, pharmacokinetics of the test substance is called linear. If the pharmacokinetic characteristics are linear, blood concentrations and pharmacokinetic parameters at other doses can be easily estimated. Therefore, it is very useful to know in terms of therapeutic

treatment whether pharmacokinetics at clinical doses indicates linearity. In many cases, linearity is examined from single-administration data at different doses. On the other hand, in a single-dose study, the half-life in the final elimination phase is sometimes hard to evaluate accurately, which makes it difficult to predict the potential for accumulation. In such cases, a repeated-dose study can be utilized.

Note 7 &

When a drug with a half-life longer than the dosing interval is repeatedly administered, the drug accumulates within the body to a higher blood concentration than with a single-dose administration. Eventually, the blood concentration reaches a plateau after repetitive administration. This is the point where the blood concentration has reached a steady state. If the ratio of parameters such as AUC, C_{max}, C_{min}, or C_{av} at the time of steady state and after single-dose administration (observed cumulative coefficient: R_{obs}) is different from the prediction based on data from single-dose studies, the following can be inferred. The theoretical value of the accumulation coefficient (R) can be calculated from compartment models and the superposition method.

If R_{obs}>R: Pharmacokinetics around the steady state is non-linear. There may be enzyme inhibition (or down-regulation 8 9 : ; < = >) by the investigational drug or its metabolites, inhibition or down-regulation of transporters, or hepatic and/or renal dysfunction caused by the investigational drug. In such cases, the effect is cumulative.

If R_{obs}<R: Pharmacokinetics around the steady state is non-linear. There may be enzyme induction by the investigational drug or its metabolites, transporter induction and insufficient solubility at the administered sites.

When the steady-state drug concentration estimated from the results of a single-dose study cannot be obtained under conditions where the drug is administered repeatedly, metabolic enzyme induction is assumed. When an unexpectedly high degree of accumulation is observed, inhibition of metabolic enzymes and toxicity of drug-clearing organs can be considered as a causal factor. Therefore, in such cases, it is necessary to clarify the underlying cause.

When linearity is not observed after single-dose administration, the data generated in a repeated-dose administration study should be interpreted in relation to the cause of non-linearity.

Note 3:

If the linearity of pharmacokinetics is not established, the proportion of metabolites and unchanged drug will be altered, and new metabolites may be detected with increasing dose. Therefore, if linearity cannot be established, careful phase I studies with doses above the clinically estimated maximum dose and evaluation by repeated-dose administration are also useful.

Note 4:

For the purpose to know the adequacy of the parameters and the validity of the incorporated model in the population pharmacokinetics approach, it is necessary to consider: " ? : @ A B

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1) whether the target population and sample size are appropriate in order to obtain sufficient information as to the expected population who will receive the drug in the future.

2) whether the number of positive patients and negative patients relative to each factor are sufficient for analysis, if the influence of such factors as concomitant use of medicines and the presence of other diseases, both of which affect pharmacokinetics, are to be discussed.

3) whether the protocol of sampling is appropriately designed in order to obtain maximum information with a minimum level of data.

4) whether the sampling plan is appropriate from the viewpoint of pharmacokinetics in the previous studies.

13. Questions and Answers

Q1 & ! Are preparations for topical application or medicines prepared using biotechnology also discussed in this document?

A1 & Although this document describes the basic principles of clinical pharmacokinetic studies, it should not be applied uniformly to all medicines. For a drug with unique properties, the choice of study items and methods is recommended based on an understanding of the basic aspects of this document; however, referral to related guidelines, if any, is also recommended. When a choice is given, the scientific appropriateness of the selection is to be stated.

Q2: The document recommends that quantitative analyses be conducted according to the principles of Good Laboratory Practice (GLP). Should as much confidence as possible be secured in the design of quantitative methods and concentration determinations, based on the spirit of the "Good Laboratory Practice Standards for Nonclinical Safety Studies (GLP)" ?

A2: Clinical pharmacokinetic studies are performed based on the "Guideline for Good Clinical Practice" (GCP), but in this guideline, no recommendations for appropriate testing facilities, assay instruments, or analysis personnel are provided. For these matters, compliance with the "Good Laboratory Practice Standards for Nonclinical Safety Studies (GLP) " is recommended.

The expression "as much confidence as possible be secured based on the spirit of the GLP" is not recommended, because it lacks definite meaning; different interpretations of this expression are possible.

As for the quantitative methods used to study the drug in question, the analyses performed currently in some facilities are based on GLP. In these facilities, the scope and contents of GLP are likely to be interpreted appropriately by practitioners. Although GLP is not applied directly in clinical pharmacokinetic studies, the following articles in GLP are regarded as references to be considered for the quantitation of a test drug and its metabolite(s): Article 5 (Personnel), Article 9 (Testing Facility), Article 10 (Instruments), Clauses 4 and 5 in Article 11 (Standard Operation Procedure), Article 14 (Reagents and Solutions), Notes 7 and 8 of Clause 1 of article 125 (Study Protocol) and Article 16 (Study Practice).

! The results of the studies performed are submitted as the principal material for a new drug application and reviewed for GCP compliance and data reliability by the Organization for Pharmaceutical Safety and Research. Accordingly, thorough concern is needed for the design, practice, analysis, report, internal review, preservation, etc.

Q3: In what situations is cross-validation needed? What is the actual method to be used, and what kind of information should be collected?
A3: The quantitative method used in a clinical pharmacokinetic study should be validated in terms of accuracy, precision, specificity, and limit of quantification, and confirmed as the appropriate method for the analysis targeted. Accordingly, even when a substance is analyzed by different methods, cross-validation is usually not needed to compare the analytical features of the methods. However, when the above specifications are not enough, and it is possible to obtain substantially different results by different methods, cross-validation is necessary. Correspondence on a case-by-case basis is recommended to obtain consistent data and to confirm the appropriateness of the obtained data for the specified purpose. Among the analytical methods with different principles (e.g. HPLC and RIA, etc.), cross-validation is usually required to confirm consistency among interpretations.

Q4: Please define "final formulation."
A4: "Final formulation" is defined as the pharmaceutical preparation that has the same formulation as the product on the market and is manufactured in the same way and on/at least, one-tenth of the scale of the actual lot of production. When a slight change in formulation is not expected to affect the pharmacokinetic properties of a drug, additional pharmacokinetic study may be considered unnecessary. For sustained-release preparations, reference to the "Guideline for the Design and Evaluation of Sustained-release Preparations (oral preparation) (1988)" is recommended.

Q5: The statement that the effect of a meal must be evaluated using the final formulation can be interpreted to mean that such pharmacokinetic data should be obtained after drug administration using the dosing regimen submitted for approval. Is this correct?
A5: In principle, the effects of a meal on an oral dose preparation are evaluated using the final formulation, irrespective of the clinical dosing regimen.

Q6: For a drug that is administered by a route other than the intravenous route, in what instance should the pharmacokinetic parameters after intravenous administration be studied? Please give a specific example. In addition, what are the methods and scope of non-clinical studies (safety studies, etc.) required prior to intravenous administration?
A6: ! Intravenous drug administration is useful for determining fundamental pharmacokinetic parameters such as clearance and volume of distribution, and for clarifying the extent of bioavailability and the role of metabolism in the liver and small intestine (first-pass effect). Accordingly, an intravenous administration study is performed, in principle, for drugs not

administered intravenously, in the case of a drug with a narrow therapeutic window, a drug with many clinically relevant adverse effects, a drug with low bioavailability, or a drug that shows individual differences and variations in systemic exposure. However, even in the above cases, an intravenous administration study is not recommended for an insoluble substance that has no proper solubilizing agent or for a substance that is potentially toxic when administered intravenously. In addition, an intravenous administration study has little meaning when the urinary recovery of the drug is over 90%. The necessity of an intravenous administration study is determined on a case-by-case basis; when it is not performed, the reason should be stated.

Clinical studies that use intravenous administration should be designed so that the plasma concentration of the drug does not exceed that determined to be safe in clinical studies that employed the clinically intended route of administration. Before a test drug is administered intravenously in humans, its intravenous toxicity in experimental animals is studied by single (bolus) or drip intravenous administration. In such studies, pharmacologic effects such as blood vessel contraction, irritation of the blood vessel wall, and hemolytic properties should be evaluated. Whether the administered drug or any drug-related precipitate is trapped in the capillary vessels of kidney, lung, liver, etc. should be also examined.

Administration by intravenous drip, while keeping the plasma concentration or systemic exposure of the drug below the toxic level determined for the clinically intended route of administration, is an actual intravenous administration method used in humans.

Q7: What do you think of the methods to ensure privacy and other rights of subjects when a pharmacokinetic study is performed based on genetic polymorphism?

A7: In the early stages of drug development, especially in studies with healthy volunteers, there are many occasions where genetic polymorphisms of drug metabolizing enzymes of participants are already known. When new genetic information is to be analyzed, the consent of the subjects should be carefully obtained after a thorough explanation. As for ethical issues of the examination, it is necessary to refer to the most current related guidelines or reports. At the present time, refer to the "Guideline for Ethical Issues for the Genomic Studies and Genetic Analysis in Human" prepared by the Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, and Ministry of Economy, Trade and Industry (March 29, 2001), "Guideline for Ethical Issues of the Study on Genetic Analysis" (Apr. 28, 2000) from Evaluation Group of Pioneering Clinical Technique in Health Science Council and "Basic principle of human genome study" (Jun. 14, 2000) from Ethics Committee on Life Science of Japanese Board for Science and Technology.

Genetic polymorphisms can be identified either by genotyping or phenotyping, but in the former case, the genotype that relates clearly to metabolic activity should be utilized.

Q8: In a situation where the distribution of an enzyme that causes a poor metabolizer (PM) phenotype for Japanese individuals has a very low frequency, is it permissible to evaluate the extent of the effect of the genetic polymorphism on pharmacokinetics in a clinical study of foreign subjects?

A8: When drug metabolism studies with human liver microsomes (or recombinant enzymes 8 9) is shown to be influenced to a great extent by a genetic polymorphism, a clinical study should be conducted to evaluate the effect of that genetic polymorphism in humans. For genetic polymorphisms of very low frequency in the Japanese population, the results of clinical studies in foreign countries are expected to provide valuable information. In this case, it should be explained in scientific terms that the study is difficult to perform in Japan, referring to reputable publications.

Q9: The time of integration of females into a clinical study at the early stage of drug development is interpreted to depend on the properties of the test drug. Is this interpretation correct?

A9: It is possible that a drug that is intended for the treatment of symptoms that occur frequently in females or for a disease specific to females will be studied clinically at the early stage in females. For other drugs, the time for integration is determined on a case-by-case basis. To determine the appropriate time, the results of safety studies outlined in the "Guideline to Timing of non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" should be consulted.

Q10: In what situations, is it useful to assay the test drug and its metabolites in feces?

A10: Assays to determine the concentration of the test drug and its metabolites in feces are often useful to evaluate drug pharmacokinetics in humans when the urinary recovery is low in spite of a high recovery indicated by the results of non-clinical studies. That is, such assays are useful when the biliary excretion ratio is estimated to be high, and when the urinary yield is very low, and the results of non-clinical studies cannot be used to predict the mass balance in humans. On the other hand, even if the urinary recovery is low, the meaning of a fecal assay would be relatively low if the clinical results coincide well with those of non-clinical studies such that the results in humans can be reliably predicted possible from the results of non-clinical studies. The necessity of performing such analyses is recommended on a case-by-case basis, depending on the pharmacokinetic properties of the compound.

Q11: In the Glossary, the example given to illustrate linearity is that the regression line for the relationship between the administered dose and AUC should pass through the origin of the coordinate axes. What are the methods and assessment criteria for the practical evaluation of linearity?

A11: When the term "linearity" is used, fulfillment of the condition stated in the Glossary is necessary. If linearity is shown between a dose-dependent pharmacokinetic parameter and dose, the pharmacokinetic analysis and prediction in clinical practice can be easily performed. Accordingly, from a practical standpoint, the interest focuses on whether there is linearity and the word "linear" is frequently misused. When the term is used in NDA document, sufficient evidence, according to the given definition of linearity, to support it is necessary.

! On the other hand, from the view of necessity in clinical practice, information as to whether the pharmacokinetic parameters of a test drug (C_{max}, AUC, etc.) are proportional to dose over the dose range relevant to clinical use (including the anticipated clinical dose) is considered important. In this case, one should perform the linearity evaluation as follows: begin with plotting the study results against the dose, with careful observation of the pattern, then estimate the regression line and assess the linearity of the line. If linearity exists between the dose and the parameter, various kinds of pharmacokinetic analyses will be performed easily. Although different methods have been used to evaluate proportionality between AUC and dose in the test range, including the (anticipated) clinical dose, there is probably no general consensus on the criterion to evaluate linearity, including extrapolation to the origin, because of differences in pharmacokinetics of test-drug, size and precision of the study, therapeutic indication, etc. Accordingly, linearity should be evaluated with the proper criteria set for each individual case by the most appropriate method selected, depending on the properties of the test drug. Consequently, if a pharmacokinetic parameter can be practically evaluated as linear for dose, it is acceptable to consider that further analysis is allowed to proceed assuming linearity. When linearity is not recognized, the degree of non-linearity is important in the dose range used for clinical practice, and a discussion of clinical relevance will be necessary. Furthermore, if the parameter change that corresponds to the dose change is accurately estimated, it will be useful for the assessment of pharmacokinetics in clinical situations.