Guidance for Industry
Population Pharmacokinetics

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

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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This guidance makes recommendations on the use of population pharmacokinetics in the drug development process to help identify differences in drug safety and efficacy among population subgroups. It summarizes scientific and regulatory issues that should be addressed using population pharmacokinetics. The guidance discusses when to perform a population pharmacokinetic study and/or analysis; how to design and execute a population pharmacokinetic study; how to handle and analyze population pharmacokinetic data; what model validation methods are available; and how to provide appropriate documentation for population pharmacokinetic reports intended for submission to the FDA. Although the information in this guidance for industry focuses on population pharmacokinetics, the principles discussed here are equally applicable to population pharmacodynamic and toxicokinetic studies.[2]

Because the analysis of drug safety and efficacy among population subgroups is a rapidly evolving area of drug development and regulation, frequent communication between the sponsor and the FDA review staff is encouraged throughout the drug development process.

Pharmaceutical industry scientists and the FDA have long been interested in the use of population pharmacokinetics/pharmacodynamics in the analysis of drug safety and efficacy among population subgroups (1). Reference is made to this subject in other FDA guidance documents, including *General Considerations for the Clinical Evaluation of Drugs* (FDA 77-3040) and in International Conference on Harmonisation (ICH) guidances, including *E4 Dose-Response Information to Support Drug Registration*, and *E7 Studies in Support of Special Populations: Geriatrics*.[3] These guidance documents support the use of special data collection and analysis methodologies, such as the population pharmacokinetic approach (population PK approach), as part of the

[1] This guidance has been prepared by the Population Pharmacokinetic Working Group of the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on population pharmacokinetics in drug evaluation. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] A separate guidance on pharmacokinetic and pharmacodynamic modeling is in preparation.

[3] A guidance for industry on general considerations for pediatric pharmacokinetic studies is in preparation.

evaluation of pharmacokinetics in drug development.

II. BACKGROUND

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest (2). Certain patient demographical, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. For example, steady-state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function who receive the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified.

Using the population PK approach in drug development offers the possibility of gaining integrated information on pharmacokinetics, not only from relatively sparse data obtained from study subjects, but also from relatively dense data or a combination of sparse and dense data. The population PK approach allows the analysis of data from a variety of unbalanced designs as well as from studies that are normally excluded because they do not lend themselves to the usual forms of pharmacokinetic analysis, such as concentration data obtained from pediatric and elderly patients, or data obtained during the evaluation of the relationships between dose or concentration and efficacy or safety.

The subjects of traditional pharmacokinetic studies are usually healthy volunteers or highly selected patients, and the average behavior of a group (i.e., the mean plasma concentration-time profile) has been the main focus of interest. Interindividual variability in pharmacokinetics has been viewed by many as a factor that needs to be minimized, often through complex study designs and control schemes, or through restrictive inclusion/exclusion criteria. In fact, the information on the variability that will occur during clinical use is critical, and it is obscured by these restrictions. Moreover, focusing on a single variable (e.g., renal function) in a traditional pharmacokinetic study makes it difficult to study interactions among variables.

In contrast to traditional pharmacokinetic evaluation, the population PK approach encompasses some or all of the following features (3):

- The collection of relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug.

- The identification and measurement of variability during drug development and evaluation.

- The explanation of variability by identifying factors of demographic, pathophysiological, environmental, or concomitant drug-related origin that may influence the pharmacokinetic behavior of a drug.

- The quantitative estimation of the magnitude of the unexplained variability in the patient population.

The magnitude of the unexplained (random) variability is important because the efficacy and safety of a drug may decrease as unexplainable variability increases. In addition to interindividual variability, the degree to which steady-state drug concentrations in individuals typically vary about their long-term average is also important. Concentrations may vary due to inexplicable day-to-day or week-to-week kinetic variability and/or due to errors in concentration measurements. Estimates of this kind of variability (residual intrasubject, interoccasion variability) are important for therapeutic drug monitoring. Knowledge of the relationship among concentration, response, and physiology is essential to the design of dosing strategies for rational therapeutics that may not necessarily require therapeutic drug monitoring.

Defining the optimum dosing strategy for a population, subgroup, or individual patient requires resolution of the variability issues discussed above. Recognition of the importance of developing optimum dosing strategies has led to a surge in the use of the population PK approach in new drug development and the regulatory process. A recent survey of 206 new drug applications and supplements reviewed by the Office of Clinical Pharmacology and Biopharmaceutics of the FDA in fiscal years 1995 and 1996 showed that almost one-quarter (i.e., 47) of the submissions contained population PK and/or pharmacodynamic reports. Because of early integration of population PK studies with clinical studies, the population PK approach provided useful safety, efficacy, and dosage optimization information for the drug label in 83 percent of the 47 submissions. In the other 17 percent of the 47 applications, the population PK approach provided results that were in agreement with previous pharmacokinetic findings although it did not yield modifications in labeling (4). Population pharmacokinetics can be useful in the drug development process and should be considered where appropriate.

III. POPULATION PK ANALYSIS

The framework for a more formal definition of population pharmacokinetics can be found in the population model of population analysis. The population model defines at least two levels of hierarchy. At the first level, pharmacokinetic observations in an individual (such as concentrations of drug species in biological fluids) are viewed as arising from an individual probability model, whose mean is given by a pharmacokinetic model (e.g., a biexponential model) quantified by individual-specific parameters, which may vary according to the value of individual-specific time-varying covariates. The variance of individual pharmacokinetic observations (intrasubject variance) is also modeled using additional individual-specific pharmacokinetic parameters. The population model employs certain inferential approaches, which focus on providing estimates of some or all of the components of variability, along with estimates of the mean parameters. At the second level, the individual parameters are regarded as random variables and the probability distribution of these (often the mean and variance, i.e., intersubject variance) is modeled as a function of individual-specific covariates. These models, their parameter values, and the use of study designs and data analysis methods designed to elucidate population pharmacokinetic models and their parameter values, are what is meant by population pharmacokinetics.

There are two common methods for obtaining estimates of the fixed-effect (mean) and of the variability: the two-stage approach and the nonlinear mixed-effects modeling approach. The two-stage approach involves multiple measurements on each subject (the data-rich situation), which will be described briefly below. The nonlinear mixed-effects modeling approach, which can be used in situations where extensive measurements will not be made on all or any of the subjects (data-sparse situation), will be the main focus of this guidance.[4]

A. The Two-Stage Approach

The traditional method of pharmacokinetic data analysis uses a two-stage approach. The first stage of this approach involves the estimation of pharmacokinetic parameters through nonlinear regression using an individual's dense concentration-time data (data-rich situation). Individual parameter estimates obtained during the first stage serve as input data for the second-stage calculation of descriptive summary statistics on the sample, typically, mean parameter estimates, variance, and covariance of the individual parameter estimates. Analysis of dependencies between parameters and covariates using classical statistical approaches (linear stepwise regression, covariance analysis, cluster analysis) can be included in the second stage. The two-stage approach, when applicable, can yield adequate estimates of population characteristics. Mean estimates of parameters are usually unbiased, but the random effects (variance and covariance) are likely to be overestimated in all realistic situations (5-8). Refinements have been proposed (e.g., global two-stage approach) to improve the two-stage approach through bias correction for the random effects covariance and differential *weighting* of individual data according to the data's quality and quantity (8-10).

The two-stage approach has been applied in the new drug development and evaluation process for more than 20 years, and because it is described elsewhere, it will not be comprehensively discussed in this document.

B. The Nonlinear Mixed-Effects Modeling Approach

When properly performed, population PK studies in patients combined with suitable mathematical/statistical analysis, for example, using nonlinear mixed-effects modeling, is a valid, and on some occasions, preferred alternative to extensive studies. In sparse data situations, where the traditional two-stage approach is not applicable because estimates of individual parameters are, a priori, out of reach, a single-stage approach, such as nonlinear mixed-effects modeling, should be used.

In the context of drug evaluation, the nonlinear mixed-effects modeling approach developed from the recognition that, if pharmacokinetics and pharmacodynamics are to be investigated in patients, pragmatic considerations dictate that data should be collected under less stringent and restrictive design conditions. This approach considers the

[4] Other approaches, such as the naive averaged-data approach, which provides mean population pharmacokinetic parameter estimates without variability estimates, are available for use, but will not be discussed.

population study sample, rather than the individual, as a unit of analysis for the estimation of the distribution of parameters and their relationships with covariates within the population. The approach uses individual pharmacokinetic data of the observational (experimental) type, which may be sparse, unbalanced, and fragmentary, in addition to, or instead of, conventional pharmacokinetic data from traditional pharmacokinetic studies characterized by rigid and extensive sampling design (dense data situation). Analysis according to the nonlinear mixed-effects model (11) provides estimates of population characteristics that define the population distribution of the pharmacokinetic (and/or pharmacodynamic) parameter (12).

In the mixed-effects modeling context, the collection of population characteristics is composed of population mean values (derived from fixed-effects parameters) and their variability within the population (generally the variance-covariance values derived from random-effects parameters). A nonlinear mixed-effects modeling approach to the population analysis of pharmacokinetic data, therefore, consists of estimating directly the parameters of the population from the full set of individual concentration values. The individuality of each subject is maintained and accounted for, even when data are sparse. The mixed-effects modeling approach is discussed in more detail and is referred to below as the population PK approach.

IV. WHEN TO USE THE POPULATION PK APPROACH

In drug development, use of the population PK approach can help increase understanding of the quantitative relationships among drug input patterns, patient characteristics, and drug disposition (12). This approach is helpful when wishing to identify factors that affect drug behavior, or explain variability in a target population. The nonlinear mixed-effects modeling approach is especially helpful in certain adaptive study designs, such as dose-ranging studies (e.g., so called titration, or effect controlled designs).

Population modeling is most likely to add value when a reasonable a priori expectation exists that intersubject kinetic variation may warrant altered dosing for some subgroups in the target population. Likely circumstances would include (1) when the population for which the drug is intended is quite heterogeneous and (2) when the target concentration window is believed to be relatively narrow.

The population PK approach can be used to estimate population parameters of a response surface model in phase 1 and late phase 2b of clinical drug development, where information is gathered on how the drug will be used in subsequent stages of drug development (12). The population PK approach can increase the efficiency and specificity of drug development by suggesting more informative designs and analyses of experiments. In phase 1 and, perhaps, much of phase 2b, where patients are sampled extensively, complex methods of data analysis may not be needed. Two-stage methods can be used to analyze the data, and standard regression methods can be used to model dependence of parameters on covariates. Alternatively, data from individual studies in phases 1 and 2b can also be pooled and analyzed using the nonlinear mixed-effects modeling approach.

The population PK approach can also be used in early phase 2a and phase 3 of drug development to gain information on drug safety (efficacy) and to gather additional information on drug pharmacokinetics in special populations, such as the elderly (12-14). This approach can also be useful in postmarketing surveillance (phase 4) studies. Studies performed during phases 3 and 4 of clinical drug development lend themselves to the use of a full population pharmacokinetic sampling study design (few blood samples drawn from several subjects at various time points (See section V). This sampling design can provide important information during new drug evaluation, regulatory decision making, and drug labeling.

V. STUDY DESIGN AND EXECUTION

The population PK approach is useful for looking at the influences of physiological as well as pathophysiological conditions on parameters of a model with a well-established structure. The qualitative aspects of the model should be well known before embarking on a population PK study. When a population PK study is proposed, certain preliminary pharmacokinetic information and the drug's major elimination pathways in humans already should be known. Preliminary studies should establish the basic pharmacokinetic model of the drug because the sparse data collected during population PK studies may not provide adequate information for discriminating among pharmacokinetic models. In addition, a sensitive and specific assay (see section IX) capable of measuring the parent drug and all metabolites of clinical relevance should be available before a population PK study is undertaken. When properly performed, population PK studies combined with suitable mathematical/statistical analysis can be a valid alternative to extensive studies.

Because it will determine the study design, the objective of a population PK study should be defined clearly from the outset. When designing a population PK study, practical design limitations, such as sampling times, number of samples per subject, and number of subjects, should be considered. Obtaining preliminary information on variability from pilot studies makes it possible through simulation (see section C, below) to anticipate certain fatal study designs, and to recognize informative ones. Optimizing the sampling design becomes particularly important when severe limitations exist on the number of subjects and/or samples per subject (e.g., in pediatric patients or the elderly) (15). Use of informative designs for population PK studies is encouraged (15-20). Such designs should include enough patients in important subgroups to ensure accurate and precise parameter estimation and the detection of any subgroup differences.

A. Sampling Designs

In the population pharmacokinetics context, three broad approaches (with increasing information content) exist for obtaining information about pharmacokinetic variability: (1) the single-trough sampling design, (2) the multiple-trough sampling design, and (3) the full population PK sampling design.

1. Single-Trough Sampling Design

In the single-trough sampling design, a single blood sample is obtained from each patient at, or close to, the trough of drug concentrations, shortly before the next dose (21), and a frequency distribution of plasma or serum levels in the sample of patients is calculated. Assuming that (1) the sample size is large, (2) the assay and sampling errors are small, and (3) the dosing regimen and sampling times are identical for all patients, a histogram of the trough screen will give a fairly accurate picture of the variability in trough concentrations in the target population. If the three conditions are not met, a histogram will not represent strict pharmacokinetic variability because the data will include other sources of random fluctuation that significantly contribute to the observed spread (22). When related to therapeutic outcome and occurrence of side effects, such histograms can provide information about the optimal concentration range of a given drug.

The relationship between patient characteristics and trough levels can be explored using simple statistical procedures, such as multiple linear regression. Although simple, the trough (pharmacokinetic) screen can yield information about apparent clearance, but not about other parameters of interest (e.g., apparent volume of distribution, half-life). Components of variability — interindividual and residual variability — cannot be separated. This method will identify, qualitatively, pharmacokinetically relevant covariates and their differences among subpopulations.

When implementing single-trough sampling, the difficulty of getting patients and physicians to adhere to the sampling strategy should be kept in mind. Compliance with at least the last two doses before trough level measurement should be sufficient for this type of study, but the drug should be dosed to steady state. Because of possible uncertainties in compliance and sample collection times, the method can be reasonably applied only to drugs dosed at intervals less than or equal to one elimination half-life, unless the timing and level of the dose can be ensured, as in inpatient studies (23). Large numbers of subjects would be needed for this type of study because the data would be noisy.

With the single-trough sampling design, it is not advisable to measure peak observations unless the drug is given intravenously or is a certain type of sustained-release formulation. The time for achieving maximum concentration depends on rates of all processes of drug disposition and may vary among subjects. Thus, the simple estimation of peak levels is subject to large uncertainty. Sampling peak levels also yields information on variability of largely irrelevant kinetic processes for drugs whose effects relate to steady-state mean concentrations, or the area under the concentration curve.

The single-trough sampling design is discussed in this guidance because it is used commonly. Considering its limitations, however, the use of this design is not encouraged except in situations where it is absolutely necessary. When single-trough sampling is implemented, the above limitations should be kept in mind.

2. Multiple-Trough Sampling Design

In the multiple-trough sampling design, two or more blood samples are obtained near the trough of steady-state concentrations from most or all patients. In addition to relating blood concentration to patient characteristics, it is possible now to separate interindividual and residual variabilities. Since patients are studied in greater detail in this design, the design requires fewer subjects, and the relationship of trough levels to patient characteristics can be evaluated with greater precision. To estimate interindividual variability in clearance, nonlinear mixed-effects modeling should be used. When using pharmacokinetic models for parameter estimation, a sensitivity analysis (24) should be done by fixing a parameter, such as absorption rate constant, to estimate other parameters and to determine the fixed parameter value that has the least effect on the estimation of the remaining parameters. Many of the drawbacks of the single-trough screen design apply here as well. Although the estimates of intersubject and residual variability may be biased or unbiased, they will not be precise unless a large number of patients are studied.

3. Full Population PK Sampling Design

The full population PK sampling design is sometimes called *experimental population pharmacokinetic design* or *full pharmacokinetic screen*. When using this design, blood samples should be drawn from subjects at various times (typically 1 to 6 time points) following drug administration (7). The objective is to obtain, where feasible, multiple drug levels per patient at different times to describe the population PK profile. This approach permits an estimation of pharmacokinetic parameters of the drug in the study population and an explanation of variability using the nonlinear mixed-effects modeling approach. The full population PK sampling design should be planned to explore the relationship between the pharmacokinetics of a drug and demographic and pathophysiological features of the target population (with its subgroups) for which the drug is being developed.

B. Importance of Sampling Individuals on More Than One Occasion

The variance of the pharmacokinetic observations of an individual about the individual-specific pharmacokinetic model on a given occasion (i.e., the intra-individual variability) can be factored conceptually into two components: (1) variability of pharmacokinetic observations due to variability of the pharmacokinetic model from occasion to occasion (interoccasion variability) and (2) variability of pharmacokinetic observations about the individual pharmacokinetic model appropriate for the particular occasion (noise; pharmacokinetic model misspecification). Some interoccasion variability can be explained by interoccasion variation in individual time-varying covariates, but the unexplained variability represents, along with the noise, the irreducible uncertainty in predicting, and therefore controlling, drug concentrations. Drugs with narrow therapeutic indices and large interoccasion variability, for example, will be very difficult to control. If a

population PK study consists of pharmacokinetic observations solely from individuals who are studied on a single occasion, the interoccasion variability will appear incorrectly in the interindividual variability term and not in the intraindividual variability term. This could lead to inappropriate optimism about the ability to control individual therapy within the therapeutic range by using feedback (e.g., therapeutic drug monitoring, or simply adjusting dose according to observed drug effects). It also could lead to a fruitless search for interindividual covariates that might explain the (spuriously inflated) interindividual variability. It is important to avoid this situation by ensuring that at least a moderate subset of subjects in a population PK study contributes data from more than one occasion. Sampling on more than one occasion may help to estimate separately the components of intraindividual variability (25, 26).

C. Simulation

Simulation is a useful tool to provide convincing objective evidence of the merits of a proposed study design and analysis (27). Simulating a planned study offers a potentially useful tool for evaluating and understanding the consequences of different study designs. Shortcomings in study design result in the collection of uninformative data. Simulation can reveal the effect of input variables and assumptions on the results of a planned population PK study. Simulation allows study designers to assess the consequences of the design factors chosen and the assumptions made. Thus, simulation enables the pharmacometrician to better predict the results of a population PK study and to choose the study design that will best meet the study objectives (16-19, 24, 28). A simulation scheme should entail repetitive simulation and appropriate analysis of data sets to control for the effect of sampling variability on parameter estimates. Alternative study designs may be simulated to determine the most informative design.

D. Study Protocol

Two types of protocol, add-on and stand-alone protocols, may be considered depending on the setting in which a population PK study is to be performed. In either case, the protocol should contain a clear statement of the population analysis objectives, as well as details of the proposed sampling design and data collection procedures. The specific pharmacokinetic parameters to be investigated should be identified in advance. If the population PK study is added on to a clinical trial (add-on study), as can be envisioned in most situations, the PK protocol should be carefully interwoven with the existing clinical protocol to ensure that it does not compromise the primary objectives of the clinical study. Investigators should be made aware of the value of including a population PK study in the clinical trial (29). When a population PK study is a stand alone, a comprehensive protocol should be prepared. The population PK study as add-on protocol and the population PK study as stand-alone protocol are discussed briefly below. A population PK study plan should also be written when a population PK study is intended to evaluate data from existing data and/or data coming from more than one study.

1. Population PK Study as Add-On Protocol

When the population PK study is an add-on to a primary clinical study, the objectives of the population PK study should be defined clearly. The objectives should not compromise the objectives of the primary clinical study. The criteria for sampling subjects and the methods for data analysis (described in the population PK study protocol) should be stated clearly. The data to be used for population analysis should be defined, including patients and subgroups to be used and covariates to be measured. The sampling design should be specified and any subpopulation stratification should be defined (30). In a multicenter trial, it may be useful to obtain extensive data from some centers and sparse data from others (3). This type of data collection can be used for informative data analysis protecting against model misspecification and should be specified in the protocol. Real-time data assembly (see section VII.A.) would permit population PK data analysis to be performed before the end of a clinical trial and would make it possible to include the results in the filing of the new drug application (NDA).

If possible, special user-friendly case report forms for investigators should be designed to meet the needs of the pharmacokinetic evaluation.

2. Stand-Alone Study Protocol

When a population PK study is a stand-alone study, the study protocol should describe the practical details of the pharmacokinetic evaluation. The primary and secondary objectives of the population PK study should be stated clearly. The secondary objectives should be those that enable the data analyst to search for the unexpected, after the primary objectives have been addressed. The sampling design, data assembly, data checking procedures, and procedures for handling missing data and data anomalies should be clearly spelled out in the protocol. The data to be used for population analysis should be defined, including patients and subgroups to be used and covariates to be measured. The sampling design should be specified and any subgroup stratification should be defined (30). If drug-drug interactions are to be characterized, the protocol should prespecify whether to determine (1) the effect of the presence or absence of a specific concomitant medication, (2) the total daily dose of the concomitant medication, or (3) the plasma concentration of the potentially interacting medication. If food effect is to be evaluated, the time of sampling in relation to food intake, and the composition of the food, should be specified in the protocol. Also, the procedure for analyzing the data (and validation when appropriate) should be specified (see section VIII.).

Population PK data analysis, as a modeling exercise, cannot be planned to the fullest detail. However, as mentioned above, the protocol should include study objectives; patient inclusion and exclusion criteria and pharmacokinetic evaluability criteria; sampling design; data handling and checking procedures; initial assumptions for modeling; a list of possible covariates to be investigated and the rationale for choosing them; and whether a sensitivity analysis and a validation procedure are envisioned. In addition, the proposed method of model building, critical for covariates inclusion and exclusion, should be described.

Time variant covariates present particular problems. In the case of such covariates, several measurements should be made during the course of the study and, if this information is found to be incomplete, model-based techniques should be used for imputation between available data (see section VII). This scenario also applies to time invariant covariates. The protocol should include a few examples of sensible methods for dealing with missing data, in terms of the data set in question, and especially for those covariates whose values may be anticipated to be frequently missing. The issue of interoccasion variability (25) should be recognized and addressed in long-term studies.

E. Study Execution

A population PK study should be conducted according to current good clinical practice (GCP) and good laboratory practice (GLP) standards. It is important to take all reasonable measures to ensure accurate information on dosing and timing of samples relative to dosing history. The sampling strategy and the recording of samples should be part of good clinical practice and the handling of samples be part of good laboratory practice. Errors in recording sampling times relative to dosing history could result in biased and imprecise parameter estimates, depending on the nature and degree of the error (19).

Every effort should be made to ensure that study subjects and clinical investigators comply with study protocol. To improve compliance, the protocol should not be overly complicated, and blood sampling times should be convenient to both clinical staff and patients. The necessity of blood sampling should be carefully explained to patients and investigators. Instructions provided to the investigators should be clear and concise. These measures should be backed up by adequate monitoring by the sponsor while the study is ongoing. Adequate resources should be available for optimal sample preparation, storage at the investigator site, and transportation and storage of biological samples prior to analysis.

Noncompliance with drug intake can be a source of confounding and may lead to inappropriate interpretation of study results (31). Special care should be taken to use methodologies that are as objective as possible to reconstruct dosage history. Communication between all parties involved is essential for the successful conduct of a population study, especially if the study is part of a large-scale clinical trial.

VI. ASSAY

Correct evaluation of pharmacokinetic data depends on the accuracy of the analytical data obtained. The accuracy of analytical data depends on the criteria used to validate the assay method and on the quality of the sample. The importance of using validated assay methods for analyzing pharmacokinetic data cannot be over emphasized. Consequently, drug and/or metabolite(s) stability, assay sensitivity, selectivity, recovery, linearity, precision, and accuracy

should be carefully scrutinized before samples are analyzed. Consideration should be given to having the assays for population PK done with minimized assay variability. To ensure quality of the sample, clinical investigators and their staff should be educated on the importance of proper labeling and handling of biological samples.

VII. DATA HANDLING

A. Data Assembly and Editing

Real-time data assembly prevents the problems that generally arise when population PK data are stored until the end of a clinical trial. Real-time data assembly permits an ongoing evaluation of site compliance with the study protocol and creates the opportunity to correct violations of study procedures and policy (32). Evaluation of pharmacokinetic data can provide the safety data monitoring board with insight into drug exposure safety evaluations and drug-drug interactions. Real-time data assembly creates the opportunity for editing the concentration-time data, drug dosing history, and covariates data in a timely manner to meet the pharmacokinetic objectives of a clinical trial (33) and to facilitate the model building process. It also allows practical analysis and development of software protocols for the final analysis, thereby saving much time in data analysis. If real-time data analysis will be implemented for an add-on population PK study, adequate policies and procedures should be in place for study blind maintenance (29).

Data editing means using a set of procedures for detecting and correcting errors in the data. The procedures should be planned before study initiation and predefined in the study protocol. Criteria for declaring data usable or unusable (e.g., time of blood sampling missing, dosing information with no associated concentrations, concentrations with missing dosing information) should be documented in the study protocol.

B. Handling Missing Data

After assembling data for population analysis, the issue of any missing covariate data should be addressed. Missing data will not automatically invalidate the results provided a good-faith effort is made to capture the missing data and adequate documentation is made regarding why data are unavailable. However, missing data represent a potential source of bias. Thus, every effort should be made to fulfill the protocol requirements concerning the collection and management of data, thereby reducing the amount of missing data. Many subjects may be rich in covariate data, and some may be missing only a small sample of covariates. Excluding all subjects with any covariate data missing in some situations will vastly decrease the sample size. Extreme caution should be taken, but in certain situations, it may be better to impute missing covariate values for some subjects rather than to delete those subjects from the data set. Some simple methods of imputation, including the use of median, mean, or mode for missing values, may be biased and inefficient when predictors are correlated (34). A better method uses maximum likelihood procedures for predicting each predictor from all other predictors.

Another method for consideration is multiple imputation, in which several imputed data sets are analyzed to remove the optimistic bias from estimates of precision caused by imputing data and treating is as though it were actually observed (35). However, the performance of imputation techniques in this context is not well-studied, nor is there a wealth of experience on their use. Moreover, imputation of missing covariates adds another layer of assumptions to the model. Imputation procedures should be described, and a detailed explanation provided of how such imputations were done and the underlying assumptions made. The sensitivity of the results of the analysis to the method of imputation of missing data should be tested, especially if the number of missing values is substantial.

Sometimes missing concentration data can become a problem in a longitudinal population PK study that is conducted for a long time. If there is a pattern to the missing data, appropriate statistical procedures should be used to address the problem. Such procedures should be described in the population PK analysis report. However, if the concentration data are missing randomly, the process that caused the missing data can be ignored and the observed data can be analyzed without regard to the missing data (36, 37).

C. Outliers

The statistical definition of an outlier is, to some extent, arbitrary. The reasons for declaring a data point to be an outlier should be statistically convincing and, if possible, prespecified in the protocol. Any physiological or study-related event that renders the data unusable should be explained in the study report. A distinction should be made between outlying individuals (intersubject variability) and outlier data points (intrasubject variability). Because of the exploratory nature of population analysis, the study protocol may not specify a procedure for dealing with outliers. In such a situation, it would be possible to perform model building on the reduced data set (i.e., the data set without outliers) to reanalyze the entire data set (including the outliers) using the final population model, and to discuss the difference in the results. Including extreme outliers is not a good practice when using least-squares or normal-theory type estimation methods, as such outliers inevitably have a disproportionate effect on estimates. Also, it is well known that for most biological phenomena, outlying observations are far more frequent than suggested by the normal distribution (i.e., biological distributions are heavy-tailed). Some robust methods of population analysis have recently been suggested, and these may allow outliers to be retained without giving them undue weight (38-40). Outliers should be specified in a separate appendix to the report, with all data available.

D. Data Type

All data along a spectrum between two extreme types of data can be used in population PK analysis. The extremes are represented by experimental data and observational data. Experimental data arise from traditional pharmacokinetic studies characterized by controlled conditions of drug dosing and extensive blood sampling. Observational data are collected, most often, as a supplement to a study designed and carried out for another

purpose. Such data are characterized by minimal control and few design restrictions (e.g., the dosing history is subject specific; the amount of pharmacokinetic data collected from each subject varies; the timing of blood sampling in relation to drug administration differs; and the number of samples per patient, typically 1 to 6, is small).

E. Data Integrity and Computer Software

Data management activities should be based on established standard operating procedures. The validity of the data analysis results depends on the quality and validity of methods and software used for data management (data entry, storage, verification, correction, and retrieval), and statistical processing. Documentation of testing procedures for the computer software used for data management should be available. It is crucial that the software used for population analysis be adequately supported and maintained.

VIII. DATA ANALYSIS

Population modeling can be used in several phases of new drug development, including the planning, designing, and analyzing of studies in the exploratory and confirmatory stages of new drug development. Thus, the protocol should describe the pharmacokinetic models to be tested. Detailed descriptions of modeling efforts should be provided, such as data visualization, model validation, and data listing (see section IX.).

Population PK data analysis can be carried out using three interwoven steps: (1) exploratory data analysis, (2) population PK model development, and (3) model validation. The data analysis plan should be defined clearly in the study protocols (see section V).

A. Exploratory Data Analysis

Exploratory data analysis isolates and reveals patterns and features in the population data set using graphical and statistical techniques. It also serves to uncover unexpected departures from familiar models. An important element of the exploratory approach is its flexibility, both in tailoring the analysis to the structure of the data and in responding to patterns that are uncovered by successive analysis steps.

Most population PK analysis procedures are based on explicit assumptions about the data, and the validity of the analyses depends upon the validity of assumptions. Exploratory data analysis techniques provide powerful diagnostic tools for confirming assumptions or, when the assumptions are not met, for suggesting corrective actions (41). Exploratory data analysis should be coupled with more sophisticated population modeling techniques in the analysis of population PK data. Any exploratory data analysis that is performed should be well described in the population PK analysis report.

B. Population PK Model Development

1. Objectives, Hypotheses, and Assumptions

The objectives of the analyses should be stated clearly. The hypotheses being investigated should be articulated clearly. It is recommended that all known assumptions inherent in the population analysis be explicitly expressed (e.g., model assumptions, including forms and distributions of interindividual random effects and residual errors) (42).

2. Model Building

The steps taken (i.e., sequence of models tested) to develop a population model (41, 43, 44) should be outlined clearly in the population analysis report to permit the reproducibility of the analysis. The criteria and rationale for model building procedures dealing with confounding, covariate, and parameter redundancy should be stated clearly. The criteria and rationale for model reduction to arrive at the final population model should be explained clearly.

3. Reliability of Results

The reliability of the analysis results can be checked by careful examination of diagnostic plots, including predicted versus observed concentration, predicted concentration superimposed on the data, and posterior estimates of parameter versus covariate values. Checking the parameter estimates, standard errors, case deletion diagnostics, and sensitivity analysis may also be appropriate. Confidence intervals (standard errors) for parameters may be obtained by using either nonparametric techniques (such as the jackknife (41)) or the profile likelihood plot (mapping the objective function (45)). The nonlinearity of the statistical model and ill-conditioning of a given problem can produce numerical difficulties and force the estimation algorithm into a false minimum. Because the maximum likelihood procedure is sensitive to bizarre observations, the stability of the model may be checked (46). It is important to evaluate the quality of the results of a population PK study or analysis for robustness. Evaluation for robustness can be approached using sensitivity analysis (45); the use of case deletion diagnostics (41, 44) is also encouraged. Evidence of robustness demonstrates that the results are reasonable and independent of the analyst.

C. Model Validation

The objective of model validation is to examine whether the model is a good description of the validation data set in terms of its behavior and of the application proposed. Validation can be defined as the evaluation of the predictability of the model developed (i.e., the model form together with the model parameter estimates) using a learning or index data set when applied to a validation data set not used for model building and parameter estimation.

Validation depends on the objective of the analysis. A model may be valid for one purpose and invalid for another. There is no right or wrong model, nor is there a right or wrong method of fitting; subjectivity, therefore, plays a large role in model choice, validation, and interpretation of results. Currently, there is no consensus on an appropriate statistical approach to validation of population PK models. The choice of a validation approach depends on the objective of the analysis because the model is both unknown and complex (subject to multiplicity of unknown covariant effects, and nonlinear). This guidance focuses on the predictive performance aspect of validation. Not all population models need to be validated. If the population PK analysis results will be incorporated in the drug label, model validation is encouraged and model validation procedures should be an integral part of the protocol. If population PK models are developed to explain variability with no dosage adjustment recommendation envisaged and to provide descriptive information for labeling, models can be tested for stability only.

Although validation methods are still being evaluated and may require further testing, two types of validation methods have been used and are discussed below. Innovative approaches are strongly encouraged.

1. Types of Validation

The first type of validation, *external validation*, is the application of the developed model to a new data set (validation data set) from another study. External validation provides the most stringent method for testing a developed model. *Internal validation*, the second type of validation, refers to the use of *data-splitting* and resampling techniques (*cross-validation* and *bootstrapping*).

Data-splitting is a useful internal validation technique for creating a validation data set to test the predictive performance of a model when it is not practical to collect new data to be used as a validation data set. The disadvantage of data-splitting is that, in general, the predictive accuracy of the model is a function of the sample size resulting from the data-splitting (47).

To maximize the predictive accuracy of data-splitting, it is recommended that the entire sample be used for model development and assessment (47). Data-splitting may not validate the final model if one desires to recombine the index and validation data sets to derive a refined model for predictive purposes. However, if data-splitting is to be used, a random subset of the data (two-thirds, i.e., the index data set) should be used for model building, and the remaining data should be used for model validation. If the index-set survives the validation procedure, the index and validation data set can be pooled, and the final population model fitted to the combined data to determine the final model.

Another technique of internal validation is resampling. There are two ways to perform resampling: cross-validation and bootstrapping. C*ross-validation*, which is the use of repeated data-splitting, may prove beneficial because (1) the size of

the model development database can be much larger than in alternative validation methods, so that less data are discarded from the estimation process, and (2) variability is reduced by not relying on a single sample split. Due to high variation of estimates of accuracy, cross-validation is inefficient when the entire validation process is repeated (48).

Bootstrapping, another way to perform resampling, has the advantage, like cross validation, of using the entire data set for model development. Because the sample size is limited in pediatric settings where ethical and medical concerns prevent recruitment into studies, bootstrapping can be especially useful for evaluating the performance of a population model if there is no test data set (46).

2. Validation Methods

The advantages and disadvantages of various types and ways of model validation, including those employed in the literature and in applications submitted to the FDA, have been discussed above. Because the science of validating complete probability models is still evolving, data analysts are encouraged to be innovative in validation. Submissions to the Agency should contain both a detailed description of the model validation method used and a justification for why it was selected.

Some potentially useful methods for assessing the predictive performance of population models are discussed briefly here.

- **Calculating Prediction Errors on Concentrations**

  Prediction errors on concentrations are calculated as the difference between observed and model-predicted concentrations. The mean prediction error is calculated and used as a measure of accuracy, and the mean absolute error (or root mean square error) is used as a measure of precision.

  This method is best used when only one sample per subject is obtained. When more than one sample is obtained per subject, the method is inadequate because prediction errors are not independent and the performance criteria estimates are less reliable (49). However, the approach has been modified to overcome this limitation by taking into account the fact that there can be several replicate nonindependent observations in the same individual (50).

- **Calculating Standardized Prediction Errors**

  Calculation of standardized prediction errors (51) takes into account variability and correlation of observations within an individual. The mean standardized prediction error and the variance are calculated, and a test (a z-test) is performed to determine whether the mean is significantly different from zero and the standard deviation approximates 1. Confidence intervals

about the standard deviation of the standardized prediction errors can be constructed. When applied to a validation data set, this method may be overly conservative as uncertainty in parameter estimation is not taken into account.

- **Plotting Residuals Against Covariates**

Plotting residuals against covariates is a method related to the prediction errors on concentration approach; the method differs in the sense that no statistic is computed and no statistical tests are performed. A simple plot of residuals obtained by freezing the final model and predicting into a validation data set against covariates can yield information on the clinical significance of the model in terms of a covariate or subpopulation (52).

- **Validating Through Parameters**

The validation-through-parameters method (50) avoids the problems encountered in prediction error of concentrations by performing validation with model parameters. Model parameters are predicted from the validation data set with or without covariates, and bias and precision are calculated for the predictions.

- **Determining Posterior Predictive Check**

A new method, the *posterior predictive check*, may prove useful in determining whether important clinical features of present and future data sets are faithfully reproduced by the model (53, 54). However, this approach has not been widely used.

As previously stated, these methods are useful for examining the predictive performance of population models. When a test data set is not available, the bootstrap approach may be appropriate. Under that approach, the mean parameter values obtained by repeatedly fitting the final population model to a reasonable number of bootstrap replicates (e.g., at least 200 bootstrap replicates) are compared to the final population model parameter estimates obtained without bootstrap replication (46). Alternatively, cross-validation can be used. Also, the posterior predictive check may prove useful in determining whether important clinical features of present and future data sets faithfully reproduce the model (53).

Model building and validation of the results are dependent on the quality of the data used; model validation and study design are strongly linked. A linear pharmacokinetic model is only valid for a given range of doses. Thus, some imagination and reflection are required to determine the aspects of the model that are most important. Because there is no consensus on an appropriate statistical approach to the validation of a population PK model, the issue of validation may best be addressed by answering the question: Do the model deficiencies have a noticeable effect on the substantive inferences made from the model?

IX. POPULATION PK STUDY REPORT

When a population PK study is conducted as an add-on to a clinical study, all study results should be integrated. When multiple population PK studies are pooled for population analysis, a population PK analysis report should be written. The report should contain the following sections: (1) summary, (2) introduction, (3) objectives, hypotheses, and assumptions, (4) materials and methods (5) results, (6) discussion, (7) application of results, (8) appendix, and (9) electronic format files. These sections are discussed briefly here.

A. Summary

The summary should provide an overall summary of the population PK study. It should include enough information on the context of the study and an indication of the population PK study's findings and conclusions.

B. Introduction

The introduction should briefly state the general intent of the study. It should include enough background information to place the population PK study in its proper context within the drug's clinical development and indicate any special features of the population PK study.

C. Objectives, Hypotheses, and Assumptions

The objectives of the study and analysis should be stated clearly following the introduction section of the report (42) . In addition to the primary objective, any secondary objectives should be explicitly stated. If modifications are made in the objectives of the study after acceptance of the protocol, those changes should be noted in the population PK report. The report should state clearly what assumptions have been made and what hypotheses tested (see section VIII).

D. Materials and Methods

This section should contain the study protocol. In a case where data from multiple studies are pooled for analysis, the applicable study protocols should be referenced. The study design, planned sample sizes, and patient selection information, which would contain selection criteria and specific center information, should also be included. Information about the medication (the drug, dose, timing of doses, and compliance) should be documented. Assay and data collection and analysis methods should be described in detail (see below).

1. Assay

This section should contain a description of the assay method(s) used in

quantitating drug concentrations. Assay performance (quality control samples), sample chromatograms, and standard curves should also be included. The validity of the method(s) should be described.

2. Data

The report should contain the response variable and all covariate information and explain how they were obtained. The report should include a description of the sampling design used to collect the plasma samples and a description of the covariates, including their distributions and, where appropriate, the accuracy and precision with which they were measured. An electronic copy of the data set should be submitted (see section I). Data quality control and editing procedures should be described in this section.

3. Data Analysis Methods

This section should contain a detailed description of the criteria and procedures for model building and reduction, including exploratory data analysis. The following components of the data analysis method used in the study should be described here: (1) the chosen population analysis method, (2) the assumptions on model components (e.g., parameterization, random effects distributions), (3) the rationale underlying those assumptions, and (4) the chosen model-fitting method. In addition, this section should contain a description of the treatment of outliers and missing data (where applicable), as well as a flow diagram(s) (if possible) of the analysis performed and representative control/command files for each significant model building/reduction step.

E. Results

The key results of the analysis should be compiled in comprehensible tables and plots. Diagnostic plots used to develop the model and test reliability should be included. To aid interpretation and application, a thorough description of the results should be provided. Complete output of results obtained for the final population model and key intermediate steps should be included.

F. Discussion

The report should include a comprehensive statement of the rationale for model building and reduction procedures, interpretation of the results, protocol violations, and discussion and presentation of supporting graphs. The consequences of the modeling should also be discussed (e.g., suggested dosing according to body weight, relationship of creatinine clearance to drug clearance, and impact on special populations).

G. Application of Results

A discussion of how the results of the analysis will be used (e.g., to support labeling, individualize dosage, safety, or to define additional studies) should be provided. A discussion of the relationship between statistical significance and clinical relevance should also be included.

In addition, the use of graphics, often based on simulations of potential responses under the final fitted model, to communicate the application of a population model (e.g., for dosage adjustment) is recommended.

H. Appendix

The appendix should contain a representative portion of the data set used in population analysis. The programming codes along with the printouts of the results of the final model should be included, as well as any additional plots that are deemed important (see section I). Whether the analysis was performed as a result of an add-on clinical study or a stand-alone population PK study, the study protocol should be included in the appendix.

I. Electronic Files

FDA is currently finalizing a guidance for the electronic submission of NDAs, which will include information on how to submit the population PK study report in electronic format.[5] In addition, FDA is actively working on standardizing data file formats for population PK and other clinical pharmacology data and will include these standards in future versions of the electronic guidance document. In the meantime, sponsors are encouraged to submit both the reports and the data files with NDA submissions in electronic format. Until the details are included in the electronic NDA guidance document, sponsors should contact the clinical pharmcology/biopharmaceutics reviewer or team leader for guidance.

X. LABELING

Where population model parameter estimates are included in the label, the total number of subjects used for the analysis and the precision with which the parameters were estimated should be included. Where the results of the population PK analysis provide descriptive information for the label, it should be stated that the information was obtained from a population analysis. Information from population analyses used to characterize subpopulations should include the total sample size used for the analysis and the proportion of subjects belonging to the subpopulation.

[5] A draft guidance for industry, *Providing Regulatory Submission in Electronic Format — NDAs*, was published for comment in April 1998; additional guidance is under development on other submission types.

XI. USING POPULATION PK STUDIES AND ANALYSIS IN DRUG DEVELOPMENT AND SUBMISSIONS

This section provides a few examples of the type of information that can be gained from population PK studies and analysis. The wording in italics illustrates how such information could be presented in labeling. Applicants are encouraged to develop their own approaches to data presentation based on the kind of information they have been able to gather from the population PK study.

Example 1: Identification and Explanation of Pharmacokinetic Variability

The following example shows how population PK analysis can help to explain observed intersubject variability. Results indicate that both gender and body weight influence the total drug clearance (CL) while the variability in volume of distribution (Vd) can be explained by the contribution from body weight.

The influence of gender and body weight on the pharmacokinetics of drug X was studied using population PK analysis in 232 male (weight 52 to 138 kg) and 288 female (weight 49 to 116 kg) patients who underwent clinical therapy with drug X. The observed large intersubject variabilities in CL and Vd could be explained by gender and body weight as follows:

$$CL\ (ml/min) = 19.3 \times (Weight\ (kg)/75)^{2.55}\ (For\ males)$$
$$CL\ (ml/min) = 12.1 \times (Weight\ (kg)/65)^{2.75}\ (For\ females)$$

And

$$Vd\ (L) = 12 + 0.5 \times Weight\ (kg)\ (for\ both\ genders).$$

Example 2: Determining Drug PK Characteristics in Tissues Using Sparse Sampling

This example shows the application of population PK analysis in a situation where only sparse data are available from a pediatric population to provide clinically relevant information for drug X. Pharmacokinetic parameters were estimated from the data set with a kinetic model. Secondary pharmacokinetic and pharmacodynamic parameters (AUC_{MIC}, $T_{1/2}$ and T_{MIC}) were then calculated and reported.

The penetration of drug X into middle ear fluid (MEF) was investigated using population PK analysis with sparse data (1-2 samples per subject) obtained from 36 pediatric patients (2 months to 2.0 years of age) who underwent clinical therapy with drug X. The estimated area under the concentration-time curve (AUC) that was above the minimum inhibitory concentration (MIC) (AUC_{MIC}) and the half-life of drug X are 12.5 ug.hr/ml and 6.1 hours in MEF, respectively, vs. 23.7 ug.hr/ml and 3.2 hours in plasma, respectively. The calculated average times at which the concentration is above MIC (T_{MIC}) were 16.35 hours in MEF and 9.5 hours in plasma, respectively.

Example 3: Recommendation of Dose Adjustments

This example shows that dose adjustments in individual patients should be based on multiple factors such as gender, smoking habit, CLcr (creatinine clearance) and body weight. This is a example of a dosage recommendation proposed after population PK analyses of phase 3 data obtained from multi-center clinical trials.

Drug X should be dosed (in mg) according to the following table:

For Male Patients

CLcr	*>60 ml/min*		*<60 ml/min*	
Smoking	*Yes*	*No*	*Yes*	*No*
Body Weight				
<50 kg	*600*	*400*	*300*	*200*
50-60 kg	*600*	*500*	*300*	*200*
60-70 kg	*700*	*600*	*400*	*350*
70-80 kg	*800*	*700*	*450*	*350*
80 +	*1000*	*800*	*500*	*400*

For Female Patients

CLcr	*>60 ml/min*		*<60 ml/min*	
Smoking	*Yes*	*No*	*Yes*	*No*
Body Weight				
<50 kg	*500*	*300*	*200*	*150*
50-60 kg	*500*	*400*	*200*	*200*
60-70 kg	*600*	*500*	*300*	*300*
70-80 kg	*700*	*600*	*350*	*300*
80 +	*900*	*700*	*400*	*350*

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GLOSSARY

Accuracy: A measurement of error about a true value.

Bias: The degree to which the typical prediction is either too high or too low.

Bootstrapping: A computer-based data resampling method for estimating sampling variances, confidence intervals, stability of regression models, and other properties of statistics.

Covariates: Explanatory variables.

Cross-validation: A statistical method for estimating prediction error.

Data assembly: The merging of covariate information, dosing history, sample times relative to dosing history, and concentration measurements to form the population pharmacokinetic database.

Data editing: A set of procedures for detecting and correcting errors in the data.

Data-splitting: The act of partitioning available data into two portions: (1) estimation or index data set and (2) validation data set.

Exploratory data analysis: A method of data analysis that emphasizes the use of graphical and statistical techniques to isolate patterns and features in a data set.

External validation: The application of the developed model to a new data set (validation data set) from another clinical study.

Fixed effects: Parameters in the pharmacokinetic model that do not vary across subject.

Full pharmacokinetic screen: A sampling design in which blood samples are drawn from subjects at various times (typically 1 to 6 time points) following drug administration.

Imputation: The filling in of plausible and consistent values for missing data.

Interoccasion variability: Random variability in individual pharmacokinetic parameters between study occasions.

Intersubject variability: variability between subjects; measures the magnitude of random individual variablity in relation to fixed effects. Also referred to as inter-individual variability.

Internal validation: The use of data-splitting and resampling techniques (cross-validation and bootstrapping) for validation purposes.

Model validation: The evaluation of the predictability of the model (i.e., the model form together with the model parameter estimates) developed with learning or index data set on a validation data set not used for model building and estimation.

Multiple-trough screen: A sampling design in which two or more blood samples are obtained neither steady-state minimum concentration, at least from most subjects.

Nonlinear mixed-effects modeling: A nonlinear regression technique that accounts for both fixed and random effects.

Outlier: Collective term used to refer to either a contaminant or a discordant observation. A discordant observation is any observation that appears surprising or discrepant to the investigator; a contaminant observation is any observation that is not realized from the target distribution.

Population approach: The analysis of responses from individuals within a population using a defined hierarchical model, which gives the average population parameters as well as the variability across the population studies.

Population pharmacokinetics: The study of variability in plasma drug concentration between individuals when standard dosage regimens are administered.

Precision: A measurement of the typical magnitude of error about a true value.

Prediction error: The difference between an observed value and a model predicted value.

Random effects: Effects varying in a random way between subjects, between occasions, or within subject.

Real-time data assembly: The on-going collection and analysis of data obtained during clinical trails.

Residual intrasubject variability: The remaining unexplained variability in response occurring within subjects after all structural and covariate effects have been incorporated into a model.

Single-trough screen: A sampling design in which a single blood sample is obtained from each patient or some patients in a study at or close to the trough (steady-state minimum) of drug concentrations shortly before the next dose.

Simulation: The generation of data with certain types of mathematical and probabilistic models describing the behavior of the system under study.

Standard two-stage approach: A method of estimating pharmacokinetic parameters in which a pharmacokinetic model is fitted to each subject's data in the first step, and in the second step estimates of population characteristics of each parameter are computed as the empirical mean (arithmetic or geometric) and variance of the individual parameter estimates.

Traditional pharmacokinetic study: A pharmacokinetic study in which subjects are sampled intensively.

Unbalanced design: A study design in which all participating subjects do not supply the same amount of information.