Population Pharmacokinetics
Guidance for Industry

DRAFT GUIDANCE

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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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Population Pharmacokinetics
Guidance for Industry

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> This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) and biologics license applications (BLAs) in the application of population pharmacokinetic (population PK) analysis. Population PK analysis is frequently used to guide drug[2] development and inform recommendations on therapeutic individualization (e.g., through tailored dosing) (Marshall et al. 2015; Lee et al. 2011; Bhattaram et al. 2005). Adequate population PK data collection and analyses submitted in marketing applications have in some cases alleviated the need for postmarketing requirements (PMRs) or postmarketing commitments (PMCs).

This guidance includes common applications of population PK analysis to inform drug development and drug use. This list of applications is not meant to be comprehensive, but rather provides illustrative examples. This guidance also includes the FDA's current thinking on the data and model requirements needed to support regulatory decisions, recommendations to sponsors on drug labeling based on population PK analysis, and the general expectations regarding the format and content for population PK reports submitted to the Agency.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by Office of Clinical Pharmacology in the Center for Drug Evaluation (CDER) and Research and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For purposes of this guidance, references to *drugs* and *drug and biological products* includes drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or Act) (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

II. BACKGROUND

Population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among individuals (Sheiner, Rosenberg, and Marathe 1977; Grasela Jr and Sheiner 1991). Drug concentrations can vary significantly among individuals who are following the same dosing regimen. Variability can be attributed to intrinsic patient factors, such as the presence and extent of liver or renal impairment or the presence of genetic polymorphisms, or to extrinsic patient factors, such as food consumption or concomitant medications that may interact with the administered drug. In some cases, intrinsic or extrinsic factors lead to clinically relevant changes in drug concentrations that require clinical management strategies, such as a change in the dose or dosing regimen.

Intrinsic and extrinsic factors that commonly influence drug exposure are often investigated in stand-alone clinical pharmacology studies.[3] Stand-alone studies are well controlled and provide a robust assessment of these interactions. However, stand-alone studies are usually designed to focus on intrinsic and extrinsic factors with the highest potential to affect drug exposure, leaving many possible interactions unstudied. Population PK analysis typically includes data directly collected from patients, allowing an assessment of multiple intrinsic and extrinsic factors that are not otherwise evaluated in healthy volunteers. In addition, the relatively large numbers of patients included in population PK analysis may improve the precision of the estimated effect of the factors that affect drug exposures and confirm which factors do not change drug exposures.

Population PK analysis integrates all relevant PK information across a range of doses to identify factors that can affect a drug's exposure. Such information can come from studies with rich PK sampling or sparse PK sampling, after a single dose or at steady state, and from healthy individuals or the patient population. These analyses, in turn, can inform strategies to manage dosing and administration for a given subpopulation, plan subsequent studies, or support labeling.

III. APPLICATION OF POPULATION PK ANALYSIS

Sponsors seeking advice on the use of population PK analysis for drug development decisions or to answer regulatory questions are encouraged to do so at appropriate milestone meetings with the Agency. Sponsors should contact the Office of Clinical Pharmacology to discuss novel methodologies and applications of population PK analyses to inform drug development and use.

Confidence in a given population PK analysis to support an intended objective is increased by the following:

- Understanding of the drug's PK properties

[3] See IX. References for specific FDA guidances for industry that address stand-alone clinical pharmacology studies.

- Prespecified questions in the study protocol or in the data analysis plan that will be addressed by a population PK analysis

- PK data of sufficient quantity and quality that represents the indicated population and relevant subpopulations of interest

- Good model performance (i.e., the model should describe the data with acceptable bias and precision) and valid for the intended purpose

A. The Application of Population PK Analysis in Drug Development

1. Selecting Dosing Regimens To Be Tested in Clinical Trials

Population PK analyses can identify covariates that significantly impact PK variability and inform dosing regimens for testing in clinical trials to help minimize the variability of treatment response in patients. For example, an observed strong relationship between body weight and drug exposure can provide support for body weight-based dosing schemes (e.g., mg/kg dosing or categorical dosing based on body weight cutpoints). Such analyses should be combined with a robust understanding of the relationship between drug exposure and drug effect (e.g., by using pharmacodynamic biomarkers or clinical endpoints), target engagement (e.g., receptor occupancy), or drug toxicity to inform and further refine dosing.

Population PK models can also be used to simulate drug exposures that are expected to occur following doses or dosing regimens that have not been directly investigated in prior clinical studies (see section V.D for a discussion on simulation strategies). For example, a population PK analysis can be used to predict PK changes resulting from the inclusion of a loading dose, changing the dose, or altering the dosing frequency of a dosing regimen for later trials in the drug development program. In rare instances and when appropriately justified, such analyses, in conjunction with exposure-response data, have been used to approve dosing regimens that have not been directly evaluated in the clinical trials (Kimko and Peck 2010). Sponsors are recommended to seek Agency input for such applications.

2. Deriving Sample Size and Sampling Scheme Requirements to Facilitate the Reliable Estimation of Covariate Effects

Simulations with population PK models can help determine the number of patients in a subpopulation that is needed to achieve sufficient power to detect a significant covariate given a defined covariate effect size (e.g., the number of patients receiving a concomitant medication that need to be included in an analysis to detect a significant drug-drug interaction; see section III.B.2). Simulations and optimal design methods can maximize the utility of such analyses. For example, the study sample size and PK sampling schedule can be optimized so that the PK parameters can be estimated with a defined degree of precision (see section IV.B for a discussion on various sampling schedules).

3. Deriving Exposure Metrics for Conducting Exposure-Response Analysis

The importance and application of exposure-response (E-R) relationships for new drugs are outlined in the 2003 FDA guidance for industry entitled *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.[4] Population PK analysis can be used to derive patient PK exposure metrics that can be used to conduct sequential E-R analyses. Derived exposure metrics (e.g., the area under the curve (AUC), the minimum drug concentration (C_{min})) can be used as a measure of average drug exposures for a patient at steady state. The derivation of exposure metrics should account for: (1) dose interruptions or modifications; and (2) variations in a drug's pharmacokinetics with time, the disease state, or the severity of the disease.

Population PK models can predict individual patient exposures at specific time points regardless of the spread in sampling times (e.g., trough concentrations can be predicted for all subjects). When PK data are missing in a small number of subjects, population PK models can predict the most likely concentration-time profile based on the subject's individual covariates (e.g., body weight, genetic polymorphism, sex). Such predictions are useful, assuming that the residual error and the between-subject variability are low, and the effect of observed covariates on the PK properties of the drug is large (see section V.D).

Individual PK patient exposure metrics are generated based on Empirical Bayes Estimates (EBEs). When individual data are sparse or uninformative, and parameter shrinkage is high (i.e., usually greater than 20 to 30 percent), EBEs are considered less reliable (Savic and Karlsson 2009). In addition to parameter shrinkage, the reliability of individual PK patient exposure metrics is dependent on the nature of the collected PK data and the validity of model assumptions (e.g., time-invariant pharmacokinetics, model structure, dose-proportional pharmacokinetics). See section V.C for discussions on model validation and section IV for discussions regarding the adequacy of the data used for population PK analysis.

4. Pediatric Study Designs

The use of modeling and simulation to inform study designs and to optimize dose selection for pediatric patients has been outlined in the 2014 draft FDA guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.[5] Additional sample size considerations for pediatric studies have been presented in the literature (Wang et al. 2012). Population PK analysis is especially appropriate in children because it allows the use of infrequent (i.e., sparse) sampling compared to the rich sampling associated with traditional PK analyses, thus minimizing the total volume of blood sampled. Sampling windows in pediatric studies are generally expected to be wider than those of adult studies, because of the limited number of blood samples obtained from pediatric patients.

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[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] When final, this guidance will represent the FDA's current thinking on this topic.

Selecting a dosing regimen for pediatric studies can be justified through simulations using a population PK model developed with adult PK data and incorporating: (1) principles of allometry; (2) knowledge of developmental changes that can influence drug pharmacokinetics (ontogeny); and (3) data on the bioavailability of the pediatric formulation (Holford, Heo, and Anderson 2013; Barbour, Fossler, and Barrett 2014; Zhang et al. 2015; Mahmood I 2014). Including the latest understanding in the population PK model on the maturation of physiology in pediatric patients across various ages, especially in those less than 2 years old, may further improve the ability to identify appropriate pediatric dosing. It should be noted that dose selection will also require understanding of disease similarity and E-R relationships in adults and pediatrics (see the 2014 draft FDA guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*[6]).

B. Application of Population PK Analysis to Inform Drug Use

Population PK analysis using data from late-stage clinical trials, together with results from stand-alone clinical pharmacology studies, can be used to support the absorption, distribution, metabolism, and excretion (ADME) information in the drug's labeling. In certain cases, traditional PK data analysis using non-compartmental analysis (NCA) methods is not adequate. For example, it can be difficult to design a study for drugs with a long half-life that would allow the area under the concentration-time curve from zero to infinity ($AUC_{0\text{-}INF}$) to be estimated with less than 20 percent extrapolation from the area under the concentration-time curve from zero to a definite time point ($AUC_{0\text{-}t}$). Such studies should be analyzed with population PK methods (Svensson et al. 2016).

In addition, population PK analysis, together with relevant information from stand-alone studies, nested studies, or other sources, is routinely used to evaluate the effects of covariates on the PK parameters of a drug and its relevant metabolites to support dosing recommendations. The need for dose adjustments due to a covariate's effect on the drug's exposure should be interpreted in the context of the known E-R relationships for efficacy and safety. The E-R relationships should be used to establish concentration boundaries between which dose adjustments are not clinically relevant (i.e., covariate effects within these boundaries may not warrant a dose alteration; however, covariate effects outside these boundaries may require a dose modification to optimize the benefit-risk profile of the drug).

1. Specific Populations

Results from population PK analyses may be incorporated into drug product labeling to describe the PK properties in general patient populations or specific populations. Labeling in specific populations based on results from population PK analysis typically includes language describing the magnitude of the covariate effect, an assessment of the clinical relevance of the changes, and may include a recommendation on the need, or lack thereof, for dosage adjustments (see section VI for more information). Whether a covariate analysis supports the labeling statements depends on multiple factors, including the number of subjects with the covariate included in the analysis,

[6] When final, this guidance will represent the FDA's current thinking on this topic.

the range of the covariate (for continuous covariates), and the extent of available PK data (see section IV.A).

Some examples of these situations are listed below:

- Stand-alone renal or hepatic impairment studies in patients without the medical condition of interest may not be ethical with some drugs (e.g., highly toxic agents). In such cases, adequate representation of patients in clinical trials with the intrinsic factor of interest, as well as adequate PK sampling to reliably characterize the intrinsic factor effects, can allow for the use of population PK analysis to inform labeling for such patients.

- In situations where specific populations (e.g., patients with varying degrees of renal impairment) can safely be included in late-stage clinical trials, population PK analysis can be used to characterize the drug's exposure and its relationship to response and derive dosing recommendations in that population.

- Some defined specific populations are traditionally not studied in stand-alone, clinical pharmacology studies because of the lack of an a priori hypothesis of a large effect on a drugs pharmacokinetics. Instead, factors such as the influence of sex, age, body weight, or race on the pharmacokinetics of the investigational drug are often studied without stand-alone trials. Population PK analysis could conceivably be used to describe a drug's pharmacokinetics in these subgroups.

- Simulations from population PK models established from pediatric and adult data can be used to compare a drug's exposure in pediatric patients and adults to derive recommended pediatric doses for labeling.

2. Drug-Drug Interactions

Clinical DDIs (e.g., nested studies as part of a phase 3 study) may be evaluated using population PK analysis. General design considerations for nested DDI studies are found in the 2017 FDA draft guidance for industry entitled *Clinical Drug Interaction Studies - Study Design, Data Analysis, Dosing Implications, and Labeling Recommendations*.[7] Using population PK approaches to characterize the DDI potential of a drug is not without limitations, and methodological considerations for using population PK analysis to evaluate DDIs have been described elsewhere (Bonate et al. 2016; Wang et al. 2017). Specific considerations for the use of a population PK approach to evaluate DDIs include the following:

- DDIs should be characterized for individual compounds and not for therapeutic classes of drugs, although exceptions are possible (e.g., multiple proton pump inhibitors can be pooled if the interaction mechanism is pH-dependent).

[7] When final, this guidance will represent the FDA's current thinking on this topic.

- Multiple perpetrators can be pooled to form one covariate category provided that the perpetrators belong to the same class of index inhibitors/inducers (i.e., weak, moderate, or strong) as identified by the Agency. The pooled perpetrators should all have the same mechanism of interaction with similar specificity for their respective metabolizing enzymes.

- An adequate number of subjects with the concomitant medication should be included in the study. The PK sampling schedule should appropriately characterize the PK parameters of interest. Simulations can determine the number of subjects needed to detect an interaction of a defined magnitude within a given study design.

- Interactions should be investigated on all physiologically plausible structural elements of the PK model (e.g., clearance (CL/F), relative bioavailability (F_{rel}), rate of absorption).

IV. DATA USED FOR POPULATION PK ANALYSIS

Sponsors are encouraged to use all available data to support the population PK model. The sponsor should justify the omission of data from certain studies, certain individuals, or certain time points and prespecify such omissions in the data analysis plan or study protocol. The sponsor should demonstrate that the data are adequate for the purpose of the analysis in their report. For example, sponsors can conduct model-based power analyses showing that the given study design has sufficient power to detect clinically meaningful covariate relationships under the proposed population PK model (see section III.B.2).

A. Study Subjects and Covariates

Determining if the data are adequate to address the intended study question is a vital step in any population PK analysis (see section V.C). The dataset should include a sufficient number of subjects with an adequate number of PK samples at informative time points. Covariates cannot be claimed to be influential or not influential on a drug's exposure if the covariate distribution is narrow (for continuous covariates) or if the number of subjects in the category is inadequate (for categorical covariates). Many continuous covariates have established cutoff values that define category levels. If dosing recommendations are proposed for these categories, the range of the continuous covariates should preferably span the entire category and not just the upper or lower ends. An increase in the range and frequency of the covariates tends to increase the likelihood of finding a true clinically significant covariate relationship and decreases the likelihood of finding false-positive relationships (Wählby et al. 2002; Wählby, Jonsson, and Karlsson 2001).

B. PK Sampling Schedule

The precision and bias of model-derived PK parameters are dependent on multiple factors, including the number of subjects, the number of samples per subject, and the sampling schedule. As the number of samples per subject decreases, the importance of the timing of PK samples increases. For example, if the purpose of an analysis is to match C_{max} observations across populations or dosage forms, then a sufficient number of PK samples should be collected in the absorption phase. Sponsors are encouraged to prospectively plan the PK sampling schedule so that the population PK model is maximally informative.

The methodology and available software for the optimal design of the population PK model are covered in multiple reviews in the literature (Dodds, Hooker, and Vicini 2005; Nyberg et al. 2015; Ogungbenro and Aarons 2007; Ogungbenro and Aarons 2008). The list below shows some examples of sampling schedules. Depending on the purpose of the analysis, one or a combination of the listed strategies may be adequate:

- Patients are randomly assigned sampling windows that are derived based on optimal design methods. The number of samples per patient and the number of sampling windows are also determined based on optimal design methods.

- Patients randomly contribute two or more samples that, when combined, cover the entire dosing interval.

- Most patients contribute one sample at a specified time point, often immediately before the next dose.

Sponsors are encouraged to collect PK data from all patients. However, the extent of sampling per individual patient and the percentage of sampled patients should ultimately depend on the intended use of the data. For example, if the C_{max} will be used in subsequent E-R analyses, then there should be adequate sampling around the time to the maximum concentration (T_{max}) (see section III.A.3). In any situation, it is important to verify that patients with missing PK data do not differ from other patients. For example, patients with missing PK data should not have higher dropout rates because of a lack of effect or adverse events. If between-occasion variability will be estimated, multiple samples per individual at more than one occasion are needed. Ignoring large between-occasion variability can lead to biased population parameter estimates (Karlsson and Sheiner 1993).

V. DATA ANALYSIS

This section of the document provides some guiding principles on methodological aspects of population PK analysis. Further methodological considerations and good practices, including topics not covered here, have been described by others (Ette and Williams 2007; Bonate and Steimer 2013; Mould and Upton 2013; Byon et al. 2013; Tatarinova et al. 2013; Lunn et al. 2002; Schmidt and Radivojevic 2014).

A. Preliminary Examination of the Data

All population analyses should begin with an examination of the observed data. Preliminary examination of the data isolates and reveals patterns and features in the population dataset using graphical and statistical techniques and can provide powerful diagnostic tools for confirming assumptions or, when the assumptions are not met, for suggesting corrective actions (Tukey 1977; Ette and Ludden 1995). For example, correlations between highly correlated covariates may not provide unique information about the population. This scenario is often the case with, for example, body weight and creatinine clearance as calculated by the Cockcroft-Gault Equation. Relevant preliminary examination of the data should be concisely described in the population PK analysis report.

B. Model Development

Model development methods and best practice recommendations are constantly evolving. Specific advice on how to develop population PK models is beyond the scope of this guidance. However, to facilitate the regulatory review of population PK models, sponsors should explicitly describe their model development procedures (see section VII for more discussion on population PK reporting). Some aspects of model development that are important for regulatory review are provided below:

- Model development issues can be addressed through several valid approaches, each with its own benefits and drawbacks. For example, covariate analysis can be performed based on several approaches or their possible combinations (e.g., stepwise covariate analysis, full covariate model approach, the Lasso) (Wählby, Jonsson, and Karlsson 2002; Gastonguay 2004; Ribbing et al. 2007). In such cases, sponsors should justify why a particular approach was used.

- Covariate-parameter relationships can be established based on current knowledge of biology, physiology, or allometric principles.

- Issues regarding missing data, including missing covariates and data below the limit of quantification (LOQ), should be addressed with appropriate analysis methods (Beal 2001; Bergstrand and Karlsson 2009; Johansson and Karlsson 2013; Keizer et al. 2015). The sponsor should justify their methodological approach with regard to missing data and outliers and provide a sensitivity analysis.

- The sponsor should distinguish between outlying individuals and outlier data points. Individual data points that are suspected outliers could be omitted during the model development process. However, the sponsor should investigate the influence of the outliers on the final parameter estimates by refitting the final model to the complete dataset. Removal of suspected outlying individuals is generally discouraged unless the reason for the outlier is a protocol violation or other human error. Sponsors should specify how outliers are identified and handled in the analysis. The reasons for declaring a data point to be an outlier should be prespecified in the data analysis plan. For example, data points with a weighted residual greater than five could be considered outliers in some cases. The number of excluded outliers should be kept at a minimum and clearly documented in reports and datasets.

C. Model Validation

Model validation is a critical step for any population PK analysis and should be conducted to examine whether the developed model can sufficiently characterize the observed data and generate reliable modeling and simulation results to meet the needs of the analysis. No single model validation method is generally sufficient to evaluate all components of a model. Several methods are generally needed so that the relative strengths and weaknesses of each method can complement each other. In general, models need to describe the data with an acceptable level of bias and an acceptable degree of precision. An appropriate model should be biologically plausible, consistent with current knowledge, and have mathematically identifiable parameters.

Model validation depends on the objective of the analysis and should follow a *fit-for-purpose* approach. In some cases, a model may be valid for one purpose but not for another. For example, a model with high shrinkage on CL/F may not be useful to derive individual drug exposure levels to be used in a sequential E-R analysis (see section III.A.3). However, such a model can still be useful for a covariate analysis provided that the method for covariate modeling is insensitive to shrinkage.

Submissions to the Agency should contain both a detailed description of the model validation methods used and an explanation of why those methods were selected (see section VII.A).

1. Common Approaches for Model Validation

Procedures for conducting a thorough model validation are continuously evolving, and the Agency welcomes innovations in this field. Several common methods of model validation are reported in literature (Karlsson and Savic 2007; Byon et al. 2013). Some of these methods are discussed in the sections below.

Basic goodness-of-fit (GOF) plots illustrate how well the model describes the observed data. GOF plots are also used to evaluate model assumptions (e.g. normality of the random effects) and to guide model development. Although GOF plots can show that the overall fitting is acceptable, additional evaluation of the model in subgroups of patients is often necessary. For example, if the model will be used to predict drug exposures in pediatric patients, model validation should be conducted for all age groups. GOF plots that are stratified for important patient characteristics (e.g., stratified by age group or CYP polymorphisms), study design (e.g., dose or formulation), or other important variables are often more convincing of the adequate performance of a model than GOF plots of the full dataset.

The following is a list of some of the GOF plots that are considered informative:

- The dependent variable (DV) versus the individual predictions (IPRED)

- The DV versus population predictions (PRED)

- The absolute individual weighted residuals (|IWRES|) versus IPRED or time[8]

[8] Time should be evaluated as continuous time and as time after dose.

- The conditional weighted residuals (CWRES) versus PRED or time[7]

- A representative sample of IPRED, PRED and observations versus time (one plot per subject)[7]

- A histogram or Quantile-Quantile (Q-Q) plot of random effects

- The correlations between random effects

- The random effects versus covariates[9]

Individual parameters, IPRED and IWRES, tend to shrink towards the population estimate in individuals with few observations. When shrinkage is high (usually greater than 20-30 percent), diagnostic plots that rely on EBEs, IPRED, or IWRES can become uninformative, and correlations between random effects and covariates can be obscured (Savic and Karlsson 2009). Furthermore, high shrinkage may limit the value of using individual post hoc estimates for E-R analysis (see section III.A.3). Simulation-based, diagnostic plots are not affected by shrinkage in a similar manner and can be more informative for diagnostic purposes when shrinkage is high. There are several available simulation-based diagnostics, including, but not limited to, Visual Predictive Check (VPC), the prediction corrected VPC (pcVPC), and the Numerical Predictive Check (NPC) (Bergstrand et al. 2011).

GOF criteria can also be reflected by some numerical metrics, such as the estimate of a parameter's precision. Estimates of parameter precision can provide valuable information regarding the adequacy of the data to support that parameter. Parameter uncertainty can be estimated through several methods, including bootstrap procedures, log-likelihood profiling, or using the asymptotic standard errors of parameter estimates. In addition to parameter uncertainty, it is important to compare parameter point estimates with previous analyses and to evaluate the physiological plausibility of the point estimates. Another useful numerical metric to evaluate models is the condition value. A condition number (the ratio of the largest and the smallest eigenvalue) over 1000 indicates that the observed data cannot support the estimation of one or several parameters (Montgomery, Vining, and Peck 2012). Over-parameterized models can be simplified and updated as additional data becomes available.

Performance of the model can be checked against a set of test data, either internal or external. The validation approach mentioned above relies on the data used for model building, hence is considered as internal validation. External validation, on the other hand, relies on the data not used for model building. Data collected in a drug development program can be split into a model building dataset and a testing dataset. The testing dataset is commonly used for external validation. Data splitting is a powerful method for model evaluation. However, before deciding on a data splitting approach, sponsors should consider the potential impact of the loss of data on the model's power to detect covariate relationships and estimate parameters with an acceptable degree of precision.

[9] This plot is most informative when it is compared before and after the inclusion of covariates.

There is an additional level of uncertainty when the purpose of the model is to simulate PK profiles for scenarios that are beyond those that have been clinically studied. Such uncertainty can be addressed by a sensitivity analysis of the parameter estimates and their impact on the metric used to inform a decision (Kimko and Peck 2010).

D. Simulations Based on Population PK Models

Simulations should be based on protocols that outline the simulation study to be performed. The level of detail in the protocol should correspond to the complexity and impact of the question the simulation addresses. Models used for simulations should be validated to address the specific question the simulation study is trying to answer. Although a model can have been previously used and validated, it needs to be revalidated if the new purpose is different from the original purpose. Depending on the purpose of the model, various levels of uncertainty and variability can be added to the simulations. Some examples are discussed below.

1. Simulations Based on Fixed-Effect Estimates

In their simplest form, simulations are used to illustrate the drug-concentration profile for a typical individual. Such simulations are based on the typical estimates of the fixed-effect parameters. Note that predictions based on typical parameter estimates do not correspond to mean predictions. Mean predictions are obtained by calculating the mean concentration-time profiles based on simulations with interindividual variability in population PK parameters and residual error.

2. Simulations Based on Uncertainty of Fixed-Effect Estimates

Uncertainty in parameter estimates can be accounted for if the desire is to illustrate the probability of the typical subject's drug exposure to reach or stay above a specific cutoff point or if one wishes to illustrate the effect of covariates. For example, forest plots that illustrate the effect of covariates on AUC or other parameters can be generated based on simulations with uncertainty in fixed-effect parameters, thereby facilitating the interpretation of the relative importance of covariates on exposure. These types of simulations are also useful to evaluate the performance of new dosing regimens for testing in future trials. Additionally, simulations with parameter uncertainty can be used to graphically illustrate the effect of parameter precision on PK profiles.

3. Simulations Based on Estimates of Between-Subject Variability

Between-subject variability (BSV) in PK parameters is accounted for in simulations when the purpose is to show the range of individual predictions of concentrations in the studied population. Residual error is added to the individual prediction when the range of observed concentrations is the main interest.

If the purpose is to predict the observed concentration range of a future population, then uncertainty in the fixed-effect parameters should be accounted for in addition to the residual error and the BSV.

The correlation between random effects should be accounted for to avoid unrealistic parameter combinations in subjects. Simulations that account for BSV and include covariate effects should be conducted in a population with realistic demographic variables. Demographic variables can be obtained from databases, generated by resampling with replacement of the individuals in the original study or by sampling the covariate distributions and their correlations in the target population.

VI. LABELING BASED ON THE RESULTS OF POPULATION PK ANALYSIS

Results from population PK analysis may be presented in the CLINICAL PHARMACOLGY section and summarized in other sections of labeling, as appropriate. Other relevant labeling sections should not repeat this detailed information but rather provide a succinct description or recommendation based upon these results followed by a cross-reference to the CLINICAL PHARMACOLGY section, as appropriate. In general, there is no need to explicitly state that the information is based on population PK analysis. Recommendations for developing the CLINICAL PHARMACOLOGY section are discussed in the FDA guidance for industry entitled *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.*

VII. POPULATION PK STUDY REPORTING

This section outlines the recommended format and content for a sponsor to submit a population PK analysis in support of its drug's clinical pharmacology program. Population PK analyses can be appropriate at multiple points in the drug development process, for example in the investigational new drug application (IND), NDA, or postmarketing stages. The depth and breadth of population PK analyses at each stage can vary because of the availability or quality of clinical data.

Population PK study reports that are important for regulatory decisions should be included in the electronic common technical document (eCTD) module 5.3.3.5 and the corresponding programs, datasets and define files under the *datasets* folder within eCTD module 5.

A. Format and Content of the Population PK Report

To enable the efficient and consistent review of population PK analyses, the FDA recommends that the results from population PK analyses should be accompanied with a structured population PK report. The report should contain the following sections: (1) an executive summary, (2) a synopsis, (3) an introduction, (4) data, (5) the methods, (6) the results, (7) a discussion, (8) conclusions, and (9) an appendix (if applicable). Expected information/elements to be included in these sections is discussed briefly in Table 1. Sections of the annotated labeling that contain information based on population PK analysis should include hyperlinks to the population PK report. Additional discussion regarding reporting is available in the scientific literature (Dykstra et al. 2015).

Table 1: Expected Content in Each Section of the Population PK Study Report

Sections	Expected Content
Executive Summary	• The purpose of the analysis • The key findings that affect approval or labeling decisions • Any other recommendations based on the population PK analysis
Synopsis	• A plain language summary of objectives, data, methodology, and conclusions • A brief explanation on the sufficiency of the data to evaluate different drug exposures in relevant subpopulations • Results presented as their effect on clinically relevant drug exposures, not PK variables • Visual presentations of relevant exposure metrics to illustrate how identified subpopulations differ from the typical population
Introduction	• The background to place the population PK study in the context of the overall clinical development program • The objectives for the population PK analysis • The PK characteristics of the drug and their relevance to the final model
Data	• A description of the studies and the study data included in the population PK analysis with information on the dose, including the frequency and duration of dosing, as well as the number of subjects, number of samples, and number of LOQ samples • A distinction between all available data versus the final data used for model building and evaluation • Reasons for not including studies with available and potentially informative data, if applicable • References to the original study reports of data used for the analysis and the bioanalytical evaluation reports for each study • The LOQ should be reported for each study and bioanalytical method (if different) • Detailed demographic information • Information about the investigated covariates in tables, histograms, or matrix plots to illustrate correlations

Continued

Table 1 continued: Expected Content in Each Section of the Population PK Study Report

Sections	Expected Content
Methods	• Criteria and procedures used for model building and evaluation as well as a description of the handling of outliers and missing data • Equations for all tested covariate relationships • The choice and justification of the model-estimation method • Equations for parameter transformations, if parameters are presented in dimensions other than those in the model output file • The method for incorporating variability or parameter uncertainty or for deriving confidence intervals or prediction intervals • Detailed descriptions of simulations used to support conclusions and recommendations • Sufficient information to reproduce the analysis and to conduct supplemental analysis, when necessary • Software and electronic files used for the analysis and simulation* • Deviations from standard procedures, if applicable * Note: The FDA does not recommend or require the use of particular software for conducting population PK analysis. The sponsor should report the software used for the analysis and submit the electronic files supporting the analysis and simulations (see section VII.B below). If necessary, consult the FDA regarding the feasibility of submitting certain types of electronic files.

Results	• A description of the final model, model building steps, qualification assessments, and final parameter estimates
	• Application of the model to objectives, including the relevance of covariates on PK parameters and simulations of alternative dosing, if applicable
	• Accompanying tables and figures to place findings into context
	• Typically, tables should include:
	    o Key modeling building steps, including a description of the structural and covariate models and objective function changes
	    o A comparison of parameter estimates from the base to the final model
	    o Parameter estimates and their associated uncertainty, with variability reported as the CV% and precision reported as the percent relative standard error (RSE%) or the 95 percent confidence interval

Continued

Table 1 continued: Expected Content in Each Section of the Population PK Study Report

Results ***continued***	• Typically, figures should include:
	  ○ Diagnostic plots
	  ○ GOF plots stratified by the relevant covariates to illustrate model performance in specific subgroups

Discussion	• An interpretation of the modeling results, including discussions on:
	  ○ The adequacy or limitation of the data to support modeling conclusions
	  ○ The rationale for the modeling approach, assumption verification, and assessment of uncertainty
	  ○ Consistency or inconsistency between the results from population PK and stand-alone clinical pharmacology studies
	• An assessment of the clinical relevance of the results, including physiological plausibility and clinical significance of the identified relationships
	• An assessment of any alternative dosing regimens in the context of exposure-response analyses for safety and efficacy
	• Discussion of the drug development and regulatory decisions based on the results of the model

Conclusions	• A short summary of major findings from the analysis written in plain language
Appendix	• A run record describing the steps undertaken for the analysis • Methods and codes for generating the key figures (i.e., for figures other than standard diagnostic plots)

B. Submitting Electronic Files to the Agency

Sponsors should refer to the FDA Web site[10] for general advice on submitting data and related files (e.g., coding scripts). It is critical that all datasets and model files submitted for the base, final, and key intermediate models are the same as those used for generating the model outputs in the appendices of the report. In addition, FDA staff should be able to identify the source data for any dataset constructed using output files or postprocessed results from population PK analyses. For example, if exposure metrics from population PK analyses are included in datasets for E-R analyses, the sponsor should ensure the traceability between the population PK model output and

[10] The FDA Web Site on submitting data can be accessed at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

any postprocessing steps involved in the construction of the dataset. This can be accomplished by providing definition files, reviewer guides, or codes utilized for dataset assembly.

All conclusions made from the population PK analysis should be reproducible by the Agency with the available codes and data. It is also important to include the unique subject identifier information for each subject in the population PK dataset and ensure that the identifiers are the same in the individual clinical study report datasets. This information is vital if data integration is required between the individual level outputs (e.g. individual, post hoc estimates for CL or V_d) generated from the population PK model and the efficacy or safety datasets from the individual clinical study reports.

VIII. GLOSSARY OF SELECTED TERMS

BSV	Between-subject variability, a measure of PK variability between subjects
Covariate	An observed factor that correlates with drug exposure in patients (e.g., renal function, body weight, age, sex, genetic polymorphism)
CWRES	Conditional Weighted Residuals, a type of diagnostic
DV	Dependent variable (e.g., drug plasma concentrations)
EBE	Empirical Bayes Estimates, or individual parameter estimates in a mixed-effects model
GOF	Goodness of fit, a collection of diagnostic criteria used to evaluate model performance
IPRED	Individual Predicted Data, based on Individual Empirical Bayes parameter estimates
IWRES	Individual Weighted Residuals, a type of residual
Model evaluation	The use of various methods to evaluate model performance
Model qualification	The use of various methods to evaluate model performance for a specific purpose
NPC	Numerical Predictive Check, a GOF method related to VPC
PRED	Predicted data, based on population parameter estimates
prVPC	Prediction corrected VPC, a GOF plot related to VPC
QQ	Quantile-quantile, a type of GOF plot
Residual	The difference between the predicted and the observed value
Residual error	An estimate of the remaining unexplained variability
Shrinkage	A measure of the extent to which EBE depends on the population parameters versus the individual observed data
VPC	Visual predictive check, a type of GOF plot

IX. REFERENCES

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FDA guidances for industry:

2019 draft guidance entitled *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations*[11]

2003 final guidance entitled *Pharmacokinetics in Patients With Impaired Hepatic Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*

2010 draft guidance entitled *Pharmacokinetics in Patients With Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*[10]

2017 draft guidance entitled *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies*[10]

2017 draft guidance entitled *Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications*[10]

[11] When final, this guidance will represent the FDA's current thinking on this topic