

Design of Pediatrics Population Pharmacokinetic Studies: Study Power, Precision, and Accuracy (Draft 10/16/03)

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I. Introduction

This document is intended to provide general concepts and technical basis for developing a study design template of pediatrics population pharmacokinetics studies. Population pharmacokinetics studies can be used in NDA submissions for identifying pharmacokinetics changes due to intrinsic factors, such as age, body weight, body surface area, and gender. For pediatrics pharmacokinetics studies, the sparse sampling design is specially justified by the need of minimizing the blood volume taken from each child, and by a better study feasibility to take less samples in outpatient settings.

The quality of the results and conclusions from population pharmacokinetic studies depend very much on the quality of the study design and conduct. This document is intended to address the influence of the study design factors on the results of population pharmacokinetics studies.

The quality of a population pharmacokinetic (PPK) study design can be measured by the statistical power to achieve the study objectives, which may include (1) identifying a difference in pharmacokinetics between adults and pediatrics, and (2) accurately estimating pharmacokinetic parameters in pediatrics without bias. The results of the first objective will support whether a dose adjustment is needed for pediatrics, and the results of the second objective will provide the basis for estimating the required dose adjustment in pediatrics. This document discusses some of the key study design factors that influence the study power and prediction errors of a population pharmacokinetic study. Study simulation is an established methodology for examining the design of population pharmacokinetic studies. This document briefly describes the simulation methodologies that will be used for constructing the pediatrics PPK study design template.

Due to the complexity and interplay between different design factors, no single standard study design is recommended for all scenarios. Study simulation should be conducted on the case-by-case basis to ensure the quality of the study design and outcomes.

The contents of this document should be considered in light of the “FDA Guidance for Industry: Population Pharmacokinetics”.

II. Study Design Factors

The main objective of a pediatric pharmacokinetics (bridging) study is to provide pharmacokinetics information as a basis, in conjunction with known exposure-response relationship, for dose adjustment in the pediatric population. A decision process for recommending dose adjustment in special populations was proposed in the Clinical Pharmacology Subcommittee (CPSC) Meeting on October 23, 2002 [<http://www.fda.gov/cder/audiences>]. Based on the recommendation of the CPSC committee, the decision tree has been revised (Figure 1) and will be presented to the Committee in the April 22, 2003 meeting. The decision process requires the information to answer two key questions: first, whether there is a difference in pharmacokinetics between the special and the typical populations, and, second, whether the difference, if any, is clinically significant.

To provide sufficient information for a decision on recommending a dose adjustment for the pediatric patients, a pediatric population pharmacokinetic (PPK) study should be designed to determine whether there is a clinical significant difference in pharmacokinetics between pediatrics and adults, and to accurately estimate the pharmacokinetic parameters of the pediatric population.

Many study design factors may influence the experimental outcomes of the population pharmacokinetic (PPK) studies and their analysis results. Important PPK study design factors include the number of subjects (total and sub-population), sampling scheme (number of samples per subject, nominal sampling time, variability of actual sampling time, and whether extensive samples are taken in some subjects). In addition, the study design should also account for study conduct factors such as compliance of the patients (the variability of dosing time, whether the variability is recorded and accounted for in the analysis, consistent dosing pattern, missing doses, and whether the missing doses are recorded and accounted for in the analysis). Other non-design, drug-specific factors may also affect the quality of the study result. They include inter-subject and intra-subject variability of the pharmacokinetics.

Due to the complexity and many varieties of study designs, it is not realistic to recommend a one-size-fit-all design. However, there are some basic points for general consideration during the study design.

- The study performance should be estimated in terms of the specific study objectives, which may include (1) identifying if there is a clinical significant difference in pharmacokinetics between adults and pediatrics, and (2) accurately estimating pharmacokinetic parameters in pediatrics without bias.
- Dosing time and sampling time should be recorded during the study conduct and accounted for in the data analysis. If the deviations from the nominal times might be non-ignorable, analysis plans to deal with this are particularly important.
- Compliance is an important factor that influences the study outcomes. It should be considered in the study design and simulation, and if compliance is to be used in the

analysis of the study, the latter should include consideration of the possibility that compliance is a confounder.

- More samples per subject, and more importantly, more subjects usually provide better study performance if the study design remains otherwise the same.
- Studies with greater intra- or inter- subject variability require more samples per subject or more subjects per age group to achieve similar performance.
- Distribution of the sampling times among subjects should cover the full dosing interval as much as possible to describe the concentration-time profile.
- Fixing sampling time among subjects (ie, same sampling time for all subjects) may be inferior to randomizing sampling times, especially when the number of samples permitted per subject is insufficient to fully identify each subject’s full structural model.
- Unbalanced design (ie, different number of samples per subject or sampling time between sub-populations), if these design differences are not randomly assigned (i.e. may be informative), may bias study results.
- One-sample-per-subject design does not allow intra-subject variability and inter-subject variability to be distinguished, and may result in biased estimates of either. At least some subjects (preferably most or all) should be studied with an intra-subject design adequate to fully identify their individual model.
- To obtain good estimations of K_a , Cl and their variability, samples in the absorption and elimination phases, respectively, should be collected. Concentration of sampling times in a particular region of the dosing interval (eg, troughs in all subjects) may result in poor study outcomes.
- Study simulation is recommended as a best practice to determine study performance (power, precision, and accuracy). All relevant study design factors should be considered in the simulation.

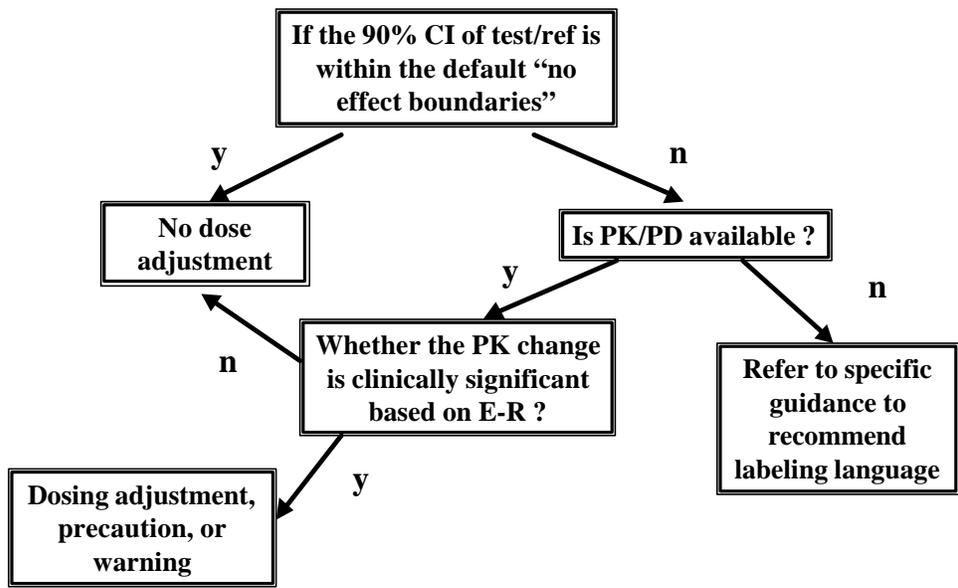


Figure 1. The revised decision tree for recommending dose adjustment in special populations (to be presented at the CPSC Meeting on April 22, 2003)

III. Methodology

Pharmacokinetic Models

Commonly used population pharmacokinetic models were described in the literature [Sheiner & Grasela, J Pharmcokinetics and Biopharmaceutics, 19(3):11S, 1991]. For example, a general pharmacokinetic structural model can be expressed in the following equation:

$$C_{ij} = f(p_{i,k}, t) + \mathbf{e}_{ij} \quad (1)$$

where C_{ij} is the plasma concentration of subject i at measurement j , $p_{i,k}$ is the k -th pharmacokinetic parameters of subject i , and \mathbf{e}_{ij} is the intra-subject variability. The individual PK parameters can be expressed in terms of population typical parameters and inter-subject variability.

$$p_{i,k} = \mathbf{q}_k + \mathbf{h}_{i,k} \quad (2)$$

where θ_k is the typical population value of p_k , and $\eta_{i,k}$ is the inter-subject variability of the parameters for subject i .

When a pharmacokinetic parameter (say, clearance) changes in a sub-population that is defined by covariate G , a covariate model can be used to describe the typical population parameter as a function of the covariate or the treatment group. For example:

$$\mathbf{q}_k = f(\mathbf{q}_n, G) \quad (3)$$

where θ_k is the typical value of pharmacokinetics parameters for the population, G is the covariate defining the sub-population, and θ_n are the parameters determining the relationship between the typical population parameter value and the covariate

Study Performance - Identifying clinically significant difference in pharmacokinetics between pediatrics and adults

The first key information to be provided by a pediatrics PPK study is whether a clinically significant difference in pharmacokinetics exists between the pediatric and adult populations (Figure 1). Various design factors may influence the power of a population pharmacokinetic study to identify a pediatric age group that may have a clinically significant difference in clearance than the adult population. To determine the study power, the objective of the study and the associated hypotheses have to be established first. Once the hypotheses are defined, they can be tested for false positive and false negative errors, ie, the estimation of study power. The hypothesis to be tested will depend on the statistical methods that will be used to compare the pediatric and adult populations. Examples of these methods include (1) pairwise comparison between

the populations, and (2) test of significance on parameter values in the covariate model (Equation 3).

For example, if the first objective of the study is restated as the following question: “When there is a clinically significant difference in clearance between adults and pediatrics, can the PPK study identify the difference?”, then the null hypothesis can be defined as:

$$H_0: \Delta Cl = 0 \quad (4)$$

where ΔCl is the difference in clearance between the pediatric and the adult populations. The alternative hypothesis can be that ΔCl is equal to a value that is considered clinically significant.

$$H_1: \Delta Cl / Cl_{\text{typical}} = x\% \quad (5)$$

where $x\%$ is the minimum difference in clearance that is considered clinically significant. The selection of the alternative hypothesis will depend on the pharmacokinetics/pharmacodynamics relationship to identify the clinical significant change in clearance. Assuming the pharmacokinetics follow Equation (1)-(3), the significance of ΔCl can be tested by fitting two models to the pharmacokinetic data: Model 1 is represented by Equations (1)-(2) and Model 2 is represented by Equations (1)-(3). The values of ΔCl is considered different from 0 by performing the likelihood ratio test between the two models.

Study simulations can be conducted to estimate the PPK study power based on the above hypotheses. A number of replicate studies and analyses are simulated with the assumption of either the null or the alternative hypotheses. The false positive and false negative rates are then estimated by counting the percentage of the replicates that show opposite results than the assumed hypothesis. The common study simulation procedure for power estimation is described later in this document.

It should also be recognized that if the null hypothesis (Equation 4) is found statistically significant based on the study outcomes, it does not necessarily indicate that the difference is clinically significant even if the study has been designed (with the alternative hypothesis, Equation 5) to detect such a difference. However, the pharmacokinetic parameter estimation should be reasonable accurate based on the study that is designed to detect a significant difference in pharmacokinetics. The second objective for the pediatric PPK study is to further ensure an accurate estimation of pharmacokinetic parameters in pediatrics, so that the dose in the population can be adequately selected.

Study Performance - Precision and accuracy of pharmacokinetic parameter estimation

The second key information to be provided by a pediatric PPK study is the estimated pharmacokinetic parameters in pediatrics (Figure 2). There are several ways for examining the precision and accuracy of parameter estimation from population

pharmacokinetics studies. Since the "true" parameter values were known in the simulations, the accuracy and precision of parameter estimation could be quantified. Both the degree of bias and the precision of estimates relative to true values are of interest and were computed.

To express bias and precision on the same scale, percentage prediction errors are computed. For each run and for each parameter, the difference between the true value θ_k and the estimated value \hat{q}_k was expressed as a percentage of the true value (i.e., percentage prediction error, %PE). Thus,

$$\%PE = [(\hat{q}_k - q_k) / q_k] \times 100\% \quad (6)$$

where k denotes the k -th parameters. A number of replicate studies can be simulated to estimate PE%. The mean %PE of all replicate studies can be used as a measure of accuracy, and SD of all %PE as a measure of precision of parameter estimation.

Precision can also be computed using:

$$Precision = SD(\%PE) \quad (7)$$

and bias can be defined as

$$Bias = E(\%PE) \quad (8)$$

Study Simulation Process

The study simulations used for study power or prediction errors estimation typical involve six main steps: (1) generating PK parameters based on observed distribution (2) simulating study design, (3) simulating the study conduct, (4) generating population PK data, (5) simulating the data analysis process, and (6) estimating power, precision, and accuracy.

Generating PK Parameters

The basic pharmacokinetic model, e.g., Equations 1-3, used to simulate the data is first assumed based on prior knowledge of the drug. Typically, only the pharmacokinetic model in adults is available at the time of designing a pediatric PPK study. A hypothesis, e.g., Equation (5), can be made to assume the minimum scenario to be identified by the PPK study, in which the pharmacokinetics of the pediatric population is clinically significantly different from that of adults.

Simulating Study Design

The following factors should be considered in the simulations: (1) study design: e.g., the number of subjects, number of samples, sampling time(s), variability of actual sampling time, whether full profile is taken in some subjects, and (2) deviation from protocol

design [Sheiner & Steimer, Annu. Rev. Pharmacol. Toxicol, 40:67, 2000]: e.g., the variability of dosing time, consistent dosing pattern, and missing doses. Pharmacokinetics covariates should also be considered in the simulation: e.g., inter-subject variability of pharmacokinetics.

Simulating Study Conduct

In addition to the above factors considered in the simulation process for study design, the following should also be considered for study conduct: whether the actual dosing time is recorded and accounted for in the analysis, and whether the missing doses are recorded and accounted for in the analysis.

Generating Population PK Data

The population pharmacokinetics data can be generated by accounting for pharmacokinetic variability and study design and study conduct factors, using the pharmacokinetic model (1)-(3). Study-related variables in individual subjects, including sampling time, concentration, dosing time, and compliance pattern, can also be generated via simulation for different study design scenarios.

Simulating Data Analysis Process

The PK Model then is fitted to the simulated data, such as Equations 1-3. Then the hypothesis, Equations 4-5, can be tested from the analysis results, and the precision and accuracy of the parameter estimation, Equations 6-8, can also be determined.

Estimating Power, Precision, and Accuracy

For each study design factor considered, a large number of replicates are simulated and fitted to the models. To estimate the study power, standard methods (such as likelihood ratio test) for estimating significance of ΔCI (Equation 3) can be used to test the Hypothesis (6) for each replicate. The number of replicates (N_p) is counted for those that resulted in significant sub-group effect. The ratio of this number (N_p) to the total number of replicates is the estimated power of the study.

The prediction errors are usually estimated by examining the mean and SD (among replicates) of %PE, bias, or precision defined in Equations (6) – (8).