

Guidance for Industry

General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products

DRAFT GUIDANCE

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TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	2
III.	STUDY DESIGN	4
IV.	METHODOLOGY.	5
	A. Standard Pharmacokinetic Study	5
	B. Population Pharmacokinetic Study	5
	C. Sample Collection	6
	D. Sample Analysis	7
	E. Covariates	7
	F. Data Analysis	7
V.	LABELING STATEMENTS	8
VI.	ETHICAL CONSIDERATIONS	8
	REFERENCES	9

GUIDANCE FOR INDUSTRY¹

General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products

I. INTRODUCTION

This guidance for industry is intended to assist applicants planning to conduct pharmacokinetic studies in pediatric populations. The guidance addresses general considerations for conducting such studies so that drug and biological products can be labeled for pediatric use.

During the past several years, the Food and Drug Administration (FDA) and others have sought ways to provide greater information about the use of drugs and biologics in children. On December 13, 1994, FDA published a final rule in the *Federal Register* that encouraged manufacturers to provide more information in product labeling about the use of a drug in the pediatric population (59 FR 64240). On August 15, 1997, FDA published proposed regulations in the *Federal Register* that would require new drugs and biologics to include labeling on how these medicines can be used safely in the pediatric population (62 FR 43899). Enactment of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-111; the Modernization Act) on November 21, 1997, further addressed the need for improved information about drug use in the pediatric population by providing incentives to sponsors for conducting pediatric studies (21 U.S.C. 355a).

The December 1994 rule recognized several methods of providing evidence to support the safe and effective use of drugs in children, including (1) evidence from adequate and well-controlled investigations of a specific pediatric indication different from the indication(s) approved for adults; (2) evidence from adequate and well-controlled investigations in children to support the same indication also approved for adults; and (3) evidence from adequate and well controlled studies in adults with additional information without new controlled clinical trials, where reliance on this evidence would depend on the conclusion that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to

¹ This guidance has been prepared by the Pediatric Subcommittee of the Medical Policy Coordinating Committee (MPCC) and the Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research (CDER), and by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on pediatric pharmacokinetic studies. 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.

permit extrapolation of the adult efficacy data to pediatric patients. As noted in the December 1994 rule, if the third approach is taken, there would ordinarily be a need for pharmacokinetic information, so that systemic exposure in adults and children could be made similar by appropriate dosing advice. If there were a concern that concentration-response relationships might be different in children, studies relating blood levels of drug to pharmacodynamic effects (PK/PD data) for the drug in the pediatric population also might be needed. Under the third approach, data from other studies supporting the safety of the drug in pediatric patients would usually be important.

In general, this guidance focuses on the pharmacokinetic information needed to select appropriate doses in the pediatric population, given the conclusion that the course of the disease in adult and pediatric populations is sufficiently similar to allow extrapolation of adult data to children and that dose/response relationships are also similar. The guidance does not consider (1) ways to establish safety and effectiveness of a drug in a pediatric population using either controlled or uncontrolled studies for safety or efficacy; (2) criteria to allow a determination that the course of a disease and the effects of a drug are the same in adults and the pediatric population; and (3) how to conduct pharmacodynamic studies to establish dose and/or concentration response relationships for efficacy and toxicity.

This document uses the definitions of pediatric populations from the 1994 rule, as follows:

- Neonate: birth to 1 month
- Infant: 1 month to 2 years
- Children: 2 to 12 years
- Adolescent: 12 years to <16 years.

The pharmacokinetics of a drug in children 16 years and older is expected to be similar to that of adults.

II. BACKGROUND

The term *pharmacokinetics* refers to the way a drug is handled by the body. Pharmacokinetic measures, such as area under the curve (AUC) and concentration at the maximum (C_{max}) and parameters calculated from those measures, such as clearance, half-life, and volume of distribution, reflect the absorption (A), distribution (D), and elimination (E) of a drug from the body. A drug can be eliminated by both metabolism (M) to one or more active and inactive metabolites and excretion of the unchanged drug. The overall set of processes is often referred to as ADME, which ultimately controls systemic exposure to a drug and its metabolites after drug administration. This systemic exposure, reflected in plasma drug and/or metabolite concentrations, is generally used to relate dose to both beneficial and adverse effects. All drugs show inter- and intra-individual variance in pharmacokinetic measures and/or parameters. Variances can sometimes be substantial. In the pediatric population, growth and developmental

changes in factors influencing ADME also lead to changes in pharmacokinetic measures and/or parameters. To achieve AUC and C_{max} values in children similar to values associated with effectiveness and safety in adults, it may be important to evaluate the pharmacokinetics of a drug over the entire pediatric age range in which the drug will be used (Gilman 1992, Rane 1976, Kauffman 1992, Butler, et al., 1994). Where growth and development are rapid, adjustment in dose within a single patient over time may be important to maintain a stable systemic exposure. Special areas of importance in planning pediatric pharmacokinetic studies are discussed in the following paragraphs.

- Absorption

Developmental changes in the pediatric population that can affect absorption include effects on gastric acidity, rates of gastric and intestinal emptying, surface area of the absorption site, gastrointestinal enzyme systems for drugs that are actively transported across the gastrointestinal mucosa, gastrointestinal permeability, and biliary function. Similarly, developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of drugs delivered via intramuscular, subcutaneous, or percutaneous absorption (Yaffe 1992).

- Distribution

Distribution of a drug may be affected by changes in body composition, such as changes in total body water and adipose tissue, that are not necessarily proportional to changes in total body weight. Plasma protein binding and tissue binding changes arising from changes in body composition with growth and development may also influence distribution (Gilman 1990).

- Metabolism

Drug metabolism usually occurs in the liver, but may also occur in the blood, gastrointestinal wall, kidney, lung, and skin. Developmental changes in metabolizing capacity can affect both absorption and elimination, depending on the degree to which intestinal and hepatic metabolic processes are involved (Brown 1989). Although developmental changes are recognized, information on drug metabolism of specific drugs in newborns, infants, and children is limited. In general, it can be assumed that children will form the same metabolites as adults via pathways such as oxidation, reduction, hydrolysis, and conjugation, but rates of metabolite formation can be different. In vitro studies performed early in drug development may thus be useful in focusing attention on metabolic pathways of elimination in both adults and children.²

² See also the guidance for industry, *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro*, April 1997.

- Excretion

Drug excretion by the kidney is controlled by glomerular filtration, tubular secretion, and tubular reabsorption. Because these processes mature at different rates in the pediatric population, age can affect systemic exposure for drugs where renal excretion is a dominant pathway of elimination. Consideration should also be given to the maturation of other excretory pathways, including biliary and pulmonary routes of excretion (Brown 1989).

- Protein Binding

Protein binding may change with age and concomitant illness. In certain circumstances, an understanding of protein binding may be needed to interpret the data from a blood level measurement and to determine appropriate dose adjustments (Rane, et al., 1971). In vitro plasma protein binding studies can determine the extent of binding of the parent and the major active metabolite(s) and identify specific binding proteins, such as albumin and alpha-1 acid glycoprotein. Optimal estimates of the degree to which protein binding is linear may be obtained by testing maximum and minimum observed concentrations.

- Pharmacodynamic Studies

Although beyond the scope of this guidance, collecting pharmacodynamic endpoints to help describe the relationship of blood concentrations to efficacy and toxicity is sometimes possible in pediatric clinical studies and should be considered. These data may allow a better understanding of whether dose and/or concentration/response relationships are essentially the same in adults and children.

- Additional Factors

In addition to the influence of growth and developmental changes on ADME, growth and development in the pediatric population can create substantial changes in body size and habitus. For this reason, pharmacokinetic measures and/or parameters for a drug may need to be described as a function of age and be related to some measure of body size, such as height, weight, and/or surface area (Kearns 1989).

III. STUDY DESIGN

In general, pharmacokinetic studies in the pediatric population should determine how the dosage regimen in the pediatric population should be adjusted to achieve approximately the same level of systemic exposure that is safe and effective in adults. Depending on the intended use of a drug in the pediatric population, studies should be performed in all pediatric age groups to allow dose adjustment within an individual over time. For drugs with linear pharmacokinetics in adults, single-dose studies often allow adequate pharmacokinetic assessment in the pediatric population.

Any nonlinearity in absorption, distribution, and elimination in adults, and any duration-of-effect-related changes would suggest the need for steady state studies in the pediatric population.

Because there may be limited information on the safety of the dose to be administered to a neonate or infant, doses in initial studies require careful consideration. Factors for consideration include (1) the relative bioavailability of the new formulation compared to the adult formulation; (2) the age of the pediatric population; (3) the therapeutic index of the drug; (4) pharmacokinetic data from the adult population; and (5) body size of the pediatric study population. Initial doses should be based on mg/kg of body weight or mg/m² of body surface area, extrapolated from adult doses. Knowledge of ADME in an adult population should be combined with an understanding of the physiologic development of the intended pediatric study population to modify the initial dose estimate. Consideration should initially be given to administering a fraction of the dose calculated from adult exposure, depending on the factors mentioned above and depending on whether there is any pediatric experience. Subsequent clinical observations and prompt assay of biological fluids for the drug and/or its metabolites should permit subsequent dose adjustment.

IV. METHODOLOGY

There are two basic approaches for performing pharmacokinetic evaluations, the standard pharmacokinetic approach and the population pharmacokinetic (PK) approach.

A. Standard Pharmacokinetic Approach

The standard pharmacokinetic approach is the usual approach for pharmacokinetic evaluation. It involves administering either single or multiple doses of a drug to a relatively small (e.g., 6-12) group of subjects with relatively frequent blood and sometimes urine sample collection. Samples are collected over specified intervals, chosen based on absorption and disposition half-lives, and subsequently assayed for concentrations, either total and/or unbound, of drug and relevant metabolites, if present. Both model-independent and model-dependent approaches can be used to establish pharmacokinetic measures, such as AUC and C_{max} and pharmacokinetic parameters, such as clearance, volume, and half-life, which are descriptive of concentration over time. Data are usually expressed as the means of the relevant measure and/or parameter and inter-individual variances. It is important in this approach to include enough subjects to give a reasonable estimate of variability. If replicate administration of the drug is provided for, either at the single dose or after multiple doses, some understanding of intra-individual variability in pharmacokinetic parameters may be obtained.

B. Population PK Approach

An alternate, and perhaps preferable, approach in many pediatric situations is the population PK approach, or study. This approach relies on infrequent (sparse) sampling

of blood from a larger population than would be used in a standard pharmacokinetic study to determine pharmacokinetic measures and/or parameters. The population PK approach is generally used in patients being given the drug therapeutically. It poses fewer issues of nontherapeutic studies in children, who are considered a vulnerable population. Another advantage of the population PK approach in pediatric populations, where blood collection is sometimes difficult, is that it allows for infrequent sampling, sometimes as few as 2-4 samples per subject, with sample collection carried out usually during routine clinic visits and performed concurrently with other blood and/or urine sampling. Because a relatively large number of patients are studied and samples can be collected at various times of day and repeatedly over time in a given subject, estimates of both population and individual means, as well as estimates of intra- and inter-subject variability can be obtained if the population PK study is properly designed. Pharmacodynamic endpoints also can be measured when collecting blood and/or urine samples so that population PK studies can also provide some understanding of concentration-response relationships for both efficacy and toxicity.

Special considerations for a population PK study include the following:

1. Where feasible, the study population, sample size, and age distribution should be adequate, either in a single study or several studies, to provide information on all pediatric age groups for which the drug is intended.
2. If other factors affecting the pharmacokinetics of the drug are to be studied (e.g., the effect of a concomitant medication or the presence or absence of a disease), sufficient numbers of subjects with and without the factor should be included in the study.
3. The sampling scheme should be carefully planned to obtain the maximum information using the minimum number of samples.
4. Some knowledge of the pharmacokinetics of the drug to be investigated from previous adult or pediatric experience may be used to develop the sampling scheme.

For sponsors interested in performing population PK studies in pediatric populations, additional general guidance is being developed.³

C. Sample Collection

Pharmacokinetic PK studies should be conducted in pediatric populations with especially

³ A guidance for industry, entitled *Population Pharmacokinetics*, was published in draft in September 1997 and currently is being finalized.

close attention to safety. Volume and frequency of blood withdrawal are often of concern in pediatric studies. Blood samples can be obtained by direct venipuncture or through the use of intravascular catheters. Because repeated venipuncture may cause pain and bruising at the puncture site, use of intravascular catheters should be considered. Given the difficulty of collecting blood samples in the pediatric population, special approaches to allow optimal times of sample collection may be useful. Volume and frequency of blood sampling can be minimized by using micro-volume drug assays and sparse-sampling techniques, respectively. These matters are especially relevant when studying neonates (Long et al., 1987). Modern assay techniques allow small sample volumes to be used to determine drug concentration (Kauffman et al., 1992), but data quality may be affected if sample volume is insufficient to allow for retesting for unusual results. Blood samples collected should come from the circulating blood volume and not from reservoirs created by catheters or other devices. The time of sample collection, proper sample transportation and storage, and sample handling techniques should be well documented. The collection of fluids such as cerebral spinal fluid (CSF) or bronchial fluids are invasive procedures that should only be used when clinically necessary. Noninvasive sampling procedures, such as urine and saliva collection, may suffice if the correlation with blood and/or plasma levels has been documented.

D. Sample Analysis

The analytical method used to quantify the drug and metabolite(s) in the biological fluid of interest should be accurate, precise, sensitive, specific, and reproducible. Ideally, the method should be relatively rapid, readily adaptable, and use only minimum sample volumes. Protein binding studies may be performed if considered important.

E. Covariates

The following covariates should ordinarily be obtained for each subject: height, weight, body surface area, gestational age and birth weight for neonates, and relevant laboratory tests that reflect the function of organs responsible for drug elimination. Concomitant and recent drug therapy should also be recorded. The relationship between these parameters and the pharmacokinetics of the drug of interest should be examined using suitable statistical techniques and study designs.

F. Data Analysis

A general objective of a pediatric population PK study is to allow adjustment in pediatric doses to achieve comparable systemic exposure measures and/or parameters to those observed in adults. Conclusions may be based on a comparison of log-transformed means for pharmacokinetic measures and/or parameters of interest. In certain instances, correlation using suitable statistical approaches may be useful in defining changes in pharmacokinetic measures and/or parameters with growth and maturation and other

covariates.

V. LABELING STATEMENTS

The labeling for a product should reflect the data pertaining to the effect of age and/or development on the pharmacokinetics and pharmacodynamics (if known) obtained from the studies conducted. If appropriate, this information may be included in the CLINICAL PHARMACOLOGY, PRECAUTIONS-Pediatric Use, and DOSAGE AND ADMINISTRATION sections of the label. The CLINICAL PHARMACOLOGY section should state differences on ADME, if any, between the adult and pediatric populations. The DOSAGE AND ADMINISTRATION section should describe dosing adjustments for pediatric patients according to age and/or body weight. An effort should be made to convey this information on a mg/kg or a mg/m² basis, as this is the most common way pediatricians calculate dosing for children. The PRECAUTIONS-Pediatric Use section should convey information on safety and activity of the drug in children according to age, even if the information is limited by small number of subjects or by brief periods of observation. These limitations should be clearly stated in this section of the label.

VI. ETHICAL CONSIDERATIONS

Both investigators and institutional review boards familiar with clinical trials in children should assist in ensuring practices that safeguard the child participant (American Academy of Pediatrics Committee on Drugs 1995). Particular attention needs to be directed to the International Conference on Harmonisation (ICH) guidance on good clinical practice,⁴ which contains a section on nontherapeutic trials in children. As noted above, population PK approaches may mitigate several problems in conducting pediatric pharmacokinetic studies.

All research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency is subject to the Department of Health and Human Services (DHHS), Policy for Protection of Human Research Subjects (45 CFR 46). The issues of consent and assent for pediatric patients enrolled in clinical trials are discussed in this DHHS regulation. If the study is performed under a U.S. investigational new drug application (IND), the informed consent (21 CFR 50) and institutional review board (21 CFR 56) regulations apply. If the study is not performed under a U.S. IND, but the data are submitted to a new drug application (NDA), a biologics license application (BLA), or a product license application (PLA), the standards of the country in which the study is performed, or the Declaration of Helsinki standards, must be met, whichever provides greater protection for the subjects of the study (21 CFR 312.120).

⁴ ICH, *E6 Good Clinical Practice: Consolidated Guideline*, May 9, 1997.

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