General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact CDER_OCP_GPT@fda.hhs.gov

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

September 2022
Clinical Pharmacology
Revision 1

General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

September 2022
Clinical Pharmacology
Revision 1

TABLE OF CONTENTS

General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 assists sponsors of investigational new drug applications (INDs) and applicants of new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), biologics license applications (BLAs) under section 351(a) of the Public Health Service Act (PHS Act), and supplements to such applications who are planning to conduct clinical studies in pediatric populations.[2,3,4] In addition, this guidance assists clinical investigators in the design and planning of, and Institutional Review Boards (IRBs) in the assessment of, clinical studies in pediatric populations.

Effectiveness, safety, or dose-finding studies in pediatric populations involve gathering clinical pharmacology information, such as information regarding a product's pharmacokinetics and pharmacodynamics, to inform dose selection and individualization. This guidance addresses general clinical pharmacology considerations for conducting studies so that the dosing and safety

[1] This guidance has been prepared by the Pediatric Working Group of the Office of Clinical Pharmacology in conjunction with the Pediatric Subcommittee of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *sponsor* refers to both sponsors and applicants.

[3] For purposes of this guidance, references to *drugs* includes drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under 351(a) of the PHS Act (42 U.S.C. 262(a)) that are regulated as drugs. Hereafter, the term *drug* will be used to refer to all such products.

[4] This guidance is applicable to BLAs submitted under section 351(a) of the PHS Act. For the Agency's thinking regarding clinical pharmacology considerations for BLAs submitted under section 351(k), see the FDA guidance entitled *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016). 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. Additionally, for information about the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act) in the context of biosimilar applications, see the FDA guidance entitled *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2)* (September 2021).

information for drugs in pediatric populations can be sufficiently characterized, leading to well-designed trials to evaluate effectiveness.

In general, this guidance focuses on the clinical pharmacology information (e.g., exposure-response, pharmacokinetics, and pharmacodynamics) that supports findings of effectiveness and safety and helps identify appropriate doses in pediatric populations. This guidance also describes how quantitative approaches (i.e., pharmacometrics) can use disease and exposure-response knowledge from relevant prior clinical studies to help design and evaluate future pediatric studies.

This guidance does not describe: (1) the standards for the approval of drugs in the pediatric population; (2) the determination that the course of a disease is the same in adults and pediatric populations; or (3) the clinical pharmacology studies for the development of vaccine therapies, blood products, or other products not regulated by the Center for Drug Evaluation and Research.

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 guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Over the past several decades, the FDA has tackled the problem of inadequate testing of drugs in pediatric patients and inadequate pediatric use information in drug labeling. The Food and Drug Administration Modernization Act of 1997 (FDAMA) addressed the need for improved information about the use of drugs in the pediatric population by establishing incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists.[5] Congress subsequently passed the Best Pharmaceuticals for Children Act (BPCA)[6] in 2002 and the Pediatric Research Equity Act (PREA) in 2003.[7] Both BPCA and PREA were reauthorized in 2007.[8] In 2010, the Biologics Price Competition and Innovation Act extended certain provisions of the BPCA to biological products.[9] In 2012, BPCA and PREA were made permanent under Title V of the FDA Safety and Innovation Act (FDASIA).[10]

[5] Public Law No. 105-115, 111 Stat. 2296 (November 21, 1997).

[6] Public Law No. 107-109, 115 Stat. 1408 (January 4, 2002).

[7] Public Law No. 108-155, 117 Stat. 1936 (December 3, 2003).

[8] Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law No. 110-85, 121 Stat. 823 (September 27, 2007).

[9] See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

[10] Public Law No. 11 2-144, 126 Stat. 993 (July 9, 2012).

Under BPCA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act and under section 351(a) of the PHS Act can obtain an additional six months of exclusivity if, in accordance with the requirements of the statute, the sponsor submits information responding to a Written Request from the Secretary relating to the use of a drug in the pediatric population.[11]

Under PREA, sponsors of certain applications and supplements filed under section 505 of the FD&C Act or section 351(a) of the Public Health Service Act are required to submit pediatric assessments, unless they receive an applicable waiver or deferral of this requirement.[12,13] If applicable, sponsors must submit a request for a deferral or waiver as part of an initial pediatric study plan (iPSP)[14] (see section V of this guidance).

The FD&C Act requires a description of pediatric study data in labeling arising from study data submitted in response to a Written Request under BPCA and/or data from studies required under PREA, whether the findings are positive, negative, or inconclusive.[15] The PREA requirements are triggered by the submission of an application or supplement for a drug under section 505 of the FD&C Act or section 351 of the PHS Act for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.[16] If a full or partial waiver is granted under PREA because there is evidence that the drug would be ineffective or unsafe in some or all pediatric populations, the information must be included in the product's labeling.[17]

This guidance addresses the clinical pharmacology considerations of any planned pediatric study, whether or not it is conducted pursuant to BPCA or PREA.[18]

III. CLINICAL PHARMACOLOGY CONSIDERATIONS

Clinical pharmacology studies in the pediatric population should be conducted in individuals with the disease which the drug is intended to treat, or in rare instances, in those who are at risk of this disease. Identifying the appropriate pediatric population to study should take into

[11] Section 505A of the FD&C Act, 21 U.S.C. 355a.

[12] Section 505B of the FD&C Act, 21 U.S.C. 355c.

[13] For more information, see the FDA draft guidance entitled *How to Comply with the Pediatric Research Equity Act* (September 2005). When final, this guidance will represent the Agency's current thinking on this topic.

[14] Section 505B(e)(2)(B) of the FD&C Act, 21 U.S.C. 355c(e)(2)(B).

[15] Section 505A(j) of the FD&C Act, 21 U.S.C. 355a(j); Section 505B(g)(2) of the FD&C Act, 21 U.S.C. 355c(g)(2).

[16] Section 505B(a)(1) of the FD&C Act, 21 U.S.C. 355c(a)(1).

[17] Section 505B(a)(5)(D) of the FD&C Act, 21 U.S.C. 355c(a)(5)(D).

[18] For more information, please see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

consideration: 1) the disease; 2) the profile of the drug under study; 3) scientific and ethical justifications; and 4) developmental changes in the pediatric population.

Sponsors should address the entire pediatric age range (birth to <17 years of age[19]) in their iPSP (waivers and deferrals of the requirements under PREA may be appropriate for specific age ranges). The pharmacokinetics of a drug is typically evaluated over the entire pediatric age range in which the agent will be used. See the FDA guidance entitled *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) for more information. The Center for Drug Evaluation and Research generally divides the pediatric population into the following groups:[20]

- Neonates: Birth up to 1 month[21,22]
- Infants: 1 month up to 2 years
- Children: 2 years up to 12 years
- Adolescents: 12 years up to younger than 17 years

If other categorizations such as physiologic categories based upon systems ontogeny or disease pathophysiology are used, they should be supported with scientific and developmental data. These categories should not be arbitrarily applied for trial enrollment but can help ensure adequate inclusion of participants across the pediatric age range.

The measurement or prediction of a drug's pharmacokinetics (exposure) and pharmacodynamics (response) is essential to the clinical pharmacology assessment. It is important to describe the exposure-response relationship of a drug in the pediatric population when possible to enhance the understanding of effective dose ranges or support the ability to extrapolate information from older pediatric participants. A pediatric drug development program should consider the time course of development of the drug metabolizing enzymes, drug excretory systems, transporters and drug target/receptors relevant (if known) to the drug being studied. This can be addressed by characterizing the pharmacokinetics and/or pharmacodynamics of the drug across the appropriate pediatric age range.

---

[19] See 21 CFR 201.57(c)(9)(iv).

[20] In 1994, the FDA revised its regulations to include more complete information about the use of a drug in pediatric populations. See the final rule on Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 FR 64240, 64241-42, (December 13, 1994). Pediatric age groups are described in the preamble to that final rule. Although the Agency has since further revised those labeling requirements (see the final rule on Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 FR 3922 (January 24, 2006)), the Agency's general thinking regarding these pediatric subpopulations has remained the same.

[21] In this guidance, as in the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018), the neonatal period is defined for the term and post-term newborn as the day of birth plus 27 days, and for the preterm newborn, as the day of birth, through the expected date of delivery plus 27 days.

[22] For more information, please see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

A. Pharmacokinetics

Pharmacokinetic (PK) measures, such as area under the curve (AUC) and maximum concentration (C_{max}), and parameters such as clearance (CL), half-life, and volume of distribution, reflect the absorption (A), distribution (D), and excretion (E) of a drug from the body. Drugs can be eliminated in the unchanged (parent) form or undergo metabolism (M) to one or more active and inactive metabolites. This overall set of processes is often referred to as ADME, which ultimately determines the systemic exposure to a drug and its metabolites after drug administration. This systemic exposure, reflected as drug or metabolite concentrations or both, is generally correlated with both beneficial and adverse drug effects. All drugs show inter- and intra-individual variability in PK measures and parameters.

In the pediatric population, growth and developmental changes in the factors that influence ADME can lead to changes in PK parameters which can lead to changes in drug response/adverse effects. Specifically, the ontogeny of drug metabolizing enzymes, transporters, and receptors should be taken into account when planning and analyzing data from pediatric PK studies.

The methodological issues in designing pediatric PK studies have been reviewed previously.[23] Special areas of importance in planning pediatric PK studies are discussed in the following paragraphs.

1. 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 drug-metabolizing enzyme systems, gastrointestinal permeability, biliary function, and transporter expression. Similarly, developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of drugs delivered by intramuscular, subcutaneous, or percutaneous absorption.[24] See section V.D for a discussion on the effect of the formulation on drug absorption.

2. Distribution

Distribution of a drug can be affected by changes in body composition, such as changes in total body water and adipose tissue, which 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 can also influence distribution. Differences between the pediatric and adult populations in blood flow to an organ, such as the brain, can also affect the distribution of a drug in the body.

---

[23] Burckart, GJ, KE Estes, R Leong, Y Mulugeta, V Tandon, J Wang, DR Abernethy, and PR Jadhav, 2012, Methodological Issues in the Design of Pediatric Pharmacokinetic Studies, Pharm Med, 26:13-22.

[24] Hong, L and S Rosenbaum, 2014, Developmental Pharmacokinetics in Pediatric Populations, J Pediatr Pharmacol Ther, 19(4):262-276.

3. Metabolism

Drug metabolism commonly occurs in the liver, but can also occur in the blood, gastrointestinal wall, kidney, lung, and skin. Developmental changes in metabolizing capacity can affect both bioavailability and elimination, depending on the degree to which intestinal and hepatic metabolic processes are involved.[25] Developmental changes in drug metabolism are well recognized, and information on the ontogeny of drug metabolism in newborns, infants, and children is now included in modeling approaches to predicting drug elimination in these groups. Both the rates of metabolite formation and the principal metabolic pathway can be different in the pediatric population compared to adults and within the pediatric population. In vitro studies performed early in drug development can be useful in identifying the metabolic pathways for a drug. See the FDA guidance entitled *In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for more information.

4. Excretion

Drug excretion by the kidney is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. Because these processes mature at different rates in the pediatric population, age can affect the systemic exposure of drugs when renal excretion is a dominant pathway of elimination. The maturation of other excretory pathways, including biliary and pulmonary routes of excretion, is also important.

5. Protein Binding

Protein binding to a drug or its metabolites can change with age and concomitant illness. In certain circumstances, an understanding of protein binding is important to interpret the data from a blood level measurement and to determine appropriate dose adjustments.[26] 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.

6. Clearance

Clearance of drugs as a function of age and body weight is generally a valuable parameter for determining the dose in the pediatric population, and drug clearance has provided a valuable tool in the assessment of pediatric clinical pharmacology studies. Scaling of drug clearance from one age group to another is a commonly used approach.

---

[25] Leeder, JS, 2004, Translating Pharmacogenetics and Pharmacogenomics into Drug Development for Clinical Pediatrics and Beyond, Drug Disc Today, 9(13):567-573.

[26] Kearns, GL, SM Abdel-Rahman, SW Alander, DL Blowey, JS Leeder, and RE Kauffman, 2003, Developmental Pharmacology - Drug Disposition, Action, and Therapy in Infants and Children, NEJM, 349;12:1157-1167.

B. Pharmacodynamics

Sponsors should collect and analyze PK and, whenever possible, pharmacodynamic (PD) data in pediatric studies to determine how the two are linked (i.e., the PK-PD or exposure-response relationship). PD data can include the effect of the drug on biomarkers or clinical endpoints for both effectiveness and safety. These measurements can allow a better understanding of whether the PK-PD relationships of the drug in pediatrics are similar to those observed in adults and can help derive rational dosing strategies in pediatrics.

If the clinical endpoint cannot be measured directly because the effect is delayed or infrequent, then the selection of an appropriate biomarker to substitute for the clinical effectiveness or toxicity endpoint is essential. Endpoint selection is a critical part of pediatric study design.[27]

C. Pharmacogenomics

Documentation that genetic differences can impact drug exposure and response is increasing,[28] but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in pediatric populations. Genotype-phenotype relationships observed in adults are not always representative of those observed in pediatric populations, particularly neonates and infants.[29] Nevertheless, if drug exposure and/or response is dependent on a well-known pharmacogenomic biomarker (e.g., cytochrome P4502D6), collecting and analyzing pharmacogenetic samples in a pediatric clinical pharmacology study could provide additional information for the interpretation of the PK and PD results. See the FDA guidance entitled *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for more information.

IV. ETHICAL CONSIDERATIONS

FDA-regulated clinical investigations are governed, in part, by IRB regulations in 21 CFR Part 56 and the human subject protection regulations in 21 CFR Part 50. The requirements in 21 CFR Part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, apply to FDA-regulated clinical pharmacology studies that enroll pediatric participants. If the proposed intervention or procedure does not offer a prospect of direct clinical benefit to the individual child, these safeguards restrict the allowable risk to which a pediatric participant can be exposed in a clinical investigation to minimal risk (21 CFR 50.51) or no more than a minor increase over

---

[27] Green, DJ, JM Burnham, P Schuette, XI Liu, BM Maas, L Yao, SK McCune, J Chen, JN van den Anker, and GJ Burckart, 2018, Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA, J Clin Pharmacol 58(7):885-890.

[28] Food and Drug Administration: Table of Pharmacogenomic Biomarkers in Drug Labeling (June 2021)), available at: https://www.fda.gov/media/124784/download (Accessed December 21, 2021).

[29] Green, DJ, P Mummaneni, IW Kim, JM Oh, M Pacanowski, and GJ Burckart, 2016, Pharmacogenomic Information in FDA-Approved Drug Labels: Application to Pediatric Patients, Clin Pharmacol Ther, 99(6):622-632.

minimal risk (21 CFR 50.53) unless the protocol is referred to the FDA by the IRB and allowed to proceed under 21 CFR 50.54 (see further description below).

Clinical pharmacology studies generally do not provide a direct clinical benefit to individual pediatric participants and must therefore present minimal risk (21 CFR 50.51) or no more than a minor increase over minimal risk (21 CFR 50.53) in order to be approved by an IRB under 21 CFR Part 50, subpart D. However, if a clinical pharmacology study offers the prospect of direct benefit to the participant, such as by ensuring that serum levels of a drug remain within the therapeutic range, then the study potentially could be approvable by an IRB under 21 CFR 50.52.

Before initiation of the clinical trial, an IRB must determine that the proposed trial is in compliance with the requirements of 21 CFR 50, subpart D.[30] However, if FDA has concerns that the rights and safety of pediatric participants may not be adequately protected, such concerns could present sufficient grounds for the FDA to impose a clinical hold because the investigation could present an unreasonable and significant risk of illness or injury to the pediatric participants (21 CFR 312.42(b)).

The assessment of a clinical pharmacology protocol under 21 CFR part 50, subpart D depends on whether the investigational drug is being administered: (1) solely for the purposes of obtaining PK data; or (2) in such a way that it offers the pediatric participant a prospect of direct clinical benefit. The two scenarios are discussed further in the case studies below.

Regardless of the scenario, administration of an investigational drug would generally be considered to represent more than minimal risk and thus would not meet the requirements for approval by an IRB under 21 CFR 50.51 (clinical investigations not involving greater than minimal risk). For IRB approval under 21 CFR 50.53, the pediatric participants must have a disorder or condition that is the focus of the clinical investigation, the investigational drug must present experiences to those subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations, and the clinical investigation must be likely to yield generalizable knowledge about the disease or condition that is of vital importance for the understanding or amelioration of that disorder or condition. For IRB approval of a clinical investigation under 21 CFR 50.52, the pediatric participants must have a prospect of direct clinical benefit from administration of the investigational product, the risk to the pediatric participants must be justified by the anticipated benefit, and the relation of the anticipated benefit to the risk must be at least as favorable to the pediatric participants as that presented by available alternative approaches. Accordingly, healthy pediatric participants (i.e., without a disorder or condition which is the focus of the research) cannot be enrolled in FDA-regulated clinical pharmacology studies unless the Commissioner determines, after consultation with a panel of experts in pertinent disciplines and opportunity for public review and comment, that the conditions in 21 CFR 50.54 are met.[31] That regulation applies to clinical investigations that are not approvable under 21 CFR 50.51, 50.52, or 50.53 but

[30] See 21 CFR 56.109(h) and 21 CFR 56.111(c).

[31] See the FDA guidance entitled *Process for Handling Referrals to FDA Under 21 CFR 50.54 - Additional Safeguards for Children in Clinical Investigations* (December 2006).

that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

A. Case 1: IRB Review of a Clinical Pharmacology Study Involving Pediatric Participants Under 21 CFR 50.53

When the investigational drug is being administered to a pediatric participant with the disease or condition for which the drug is being developed, but the intent of the study is solely for the purpose of obtaining PK data, the risk(s) presented by the investigational drug, the route of administration, and the PK sampling schedule must represent no more than a minor increase over minimal risk (21 CFR 50.53(a)) in order to be approvable by the IRB. Pediatric participants may be exposed to no more than a minor increase over minimal risk if, among other criteria, the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of that disorder or condition (21 CFR 50.53(c)). Thus, for a clinical investigation to be approved by an IRB under this category, the enrolled pediatric participant must have a disorder or condition that meets these requirements. The FDA interprets "condition" to include being at risk for the disease (disorder) based on, for example, epidemiologic, genetic, and other factors.

Furthermore, sufficient empirical data regarding the risks of the proposed interventions or procedures should be available to ascertain that the risks are no more than a minor increase over minimal risk (21 CFR 50.53(a)). If available, adult data (including dose-response information) should be considered for this purpose. When there are not enough human data to adequately characterize the risk, then the intervention or procedure generally would not be considered to present no more than a minor increase over minimal risk because the risks of the intervention or procedure would not be known with sufficient accuracy.

The risks of any blood and/or fluid sampling procedures also must represent no more than a minor increase over minimal risk (21 CFR 50.53(a)). The limited venipunctures to obtain specimens for PK analyses would generally be considered either minimal risk or a minor increase over minimal risk, and therefore could be approvable by the IRB even without the prospect of direct benefit (see 21 CFR 50.51(a) and 50.53(a)). This approach to the analysis of clinical trials is often called a *component analysis of risk*, whereby to determine the overall acceptability of the clinical investigation, the risks and anticipated direct clinical benefits of the interventions included in a protocol are analyzed individually as well as collectively.[32,33,34]

An example of a clinical pharmacology study that generally would fall under 21 CFR 50.53 is the pharmacokinetics of the oral administration of a *single dose* of an over-the-counter cough and cold product. To be enrolled in such a study, a child would either be symptomatic from an upper

[32] See the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research Involving Children: Report and Recommendations of the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, (43 FR 2084, 2086), January 13, 1978.

[33] See Preamble to the Final Rule, Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products, (78 FR12937, 12937-12950), February 26, 2013.

[34] See the FDA guidance entitled *Acute Bacterial Otitis Media: Developing Drugs for Treatment* (October 2012).

respiratory infection (URI) or be at risk for a future URI based on the presence of criteria such as the frequency of past infections, number of people living in the home, or exposure to others in a preschool or school setting. As stated above, the associated blood draws to collect PK samples would generally be considered to be minimal risk (21 CFR 50.51(a)) or no more than a minor increase over minimal risk (21 CFR 50.53(a)) and a single oral dose of the over-the-counter cough and cold product would generally be considered as no more than a minor increase over minimal risk (21 CFR 50.53(a)), thus allowing the study to proceed under 21 CFR 50.53.

If administration of a single dose of an investigational drug exceeds a minor increase over minimal risk (or there are insufficient data available to make that determination), the clinical pharmacology study either would be required to meet the requirements in 21 CFR 50.52 (as discussed below) or would require referral for review under 21 CFR 50.54 (assuming that the other requirements of that regulation were met).

B. Case 2: IRB Review of a Clinical Pharmacology Study Involving Pediatric Participants Under 21 CFR 50.52

The administration of an investigational drug with more than a minor increase over minimal risk could be approved by an IRB if the level of risk exposure is justified by a sufficient prospect of direct clinical benefit to the participants (21 CFR 50.52(a)). For example, dose-monitoring studies that ensure serum levels of an investigational drug remain within a therapeutic range generally would fall under 21 CFR 50.52 when the investigational drug presents the prospect of direct benefit to the enrolled pediatric participants and the investigational drug is administered under the protocol using a dosing regimen (including duration) that offers a sufficient prospect of direct clinical benefit to justify the risks (21 CFR 50.52(a)).

Multiple-dose PK-PD studies can be designed to offer a prospect of direct benefit, but the dose and duration of exposure to the investigational product should be sufficient to result in potential changes in the clinical manifestations of the condition or in disease-specific biomarkers that reflect a clinical benefit. For example, the duration of the PK-PD study could be extended, or perhaps combined as the lead-in phase to an efficacy trial, to provide a suitable duration of drug exposure that offers a sufficient prospect of direct clinical benefit to justify the risks.[35]

C. Ethical Justification for Pediatric Pharmacology Studies

Adequate information from clinical pharmacology studies to support pediatric dosing is critical to the development of ethically sound confirmatory trials. Inadequate pediatric dosing may lead

[35] Roth-Cline, M and RM Nelson, 2015, Ethical Considerations in Conducting Pediatric and Neonatal Research in Clinical Pharmacology, Curr Pharm Design, 21:5619-5635.

to failed pediatric clinical trials.[36] The FDA considers the public health need for adequate pediatric dosing in its assessment of the ethical propriety of proposed studies.[37,38]

V. THE PEDIATRIC STUDY PLAN DESIGN AND POINTS TO CONSIDER

A sponsor who is planning to submit a marketing application (or supplement to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an iPSP[39] unless the drug is for an indication for which orphan designation has been granted.[40] In addition, a sponsor who is planning to submit, on or after August 20, 2020, an original application for a new active ingredient that is subject to the molecularly targeted cancer drug provision of PREA (i.e., the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) is also required to submit an iPSP,[41] regardless of whether the drug is for an indication for which orphan designation has been granted.[42] By statute, a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new active ingredient for purposes of PREA.[43]

The submission of the iPSP is intended to encourage sponsors to consider pediatric studies early in product development and, when appropriate, begin planning for these studies. The FDA guidance entitled *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (July 2020) discusses the content of and process for submitting initial and amended PSPs and states that Section 10.1 (Pediatric Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Studies) should include:

---

[36] Benjamin, DK, Jr, PB Smith, P Jadhav, JV Gobburu, MD Murphy, V Hasselblad, C Baker-Smith, RM Califf, and JS Li, 2008, Pediatric Antihypertensive Trial Failures: Analysis of End Points and Dose Range, Hypertension, 51(4):834-840.

[37] See the FDA guidance entitled *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

[38] This issue is also discussed in the American Academy of Pediatrics Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. See Shaddy, R and SC Denne, 2010, Clinical Report-Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, Pediatrics,125(4):850-860.

[39] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(A) of the FD&C Act; 21 U.S.C. 355c(a)(1)(A).

[40] See section 505B(k)(1) of the FD&C Act; 21 U.S.C. 355c(k)(1).

[41] See section 505B(e)(1) of the FD&C Act; 21 U.S.C. 355c(e)(1); and section 505B(a)(1)(B) of the FD&C Act; 21 U.S.C. 355c(a)(1)(B).

[42] See section 505B(k)(2) of the FD&C Act; 21 U.S.C. 355c(k)(2).

[43] See section 505B(l) of the FD&C Act; 21 U.S.C. 355c(l).

- The type of study/study design
- The objectives of the study
- The age group and population in which the study will be conducted
- The pediatric formulation(s) to be used in the study
- The dose ranges to be used in the PK studies
- The endpoints and justification (PK parameters; PD parameters)
- The existing or planned modeling and simulation to support dose selection and/or study design, data analysis, and interpretation for planned pediatric studies
- Any planned pharmacogenomic analyses
- A justification for the sample size

When designing pediatric clinical studies, sponsors should be mindful that modeling and simulation and pharmacologic considerations are often critical for the successful completion of a study. Modeling and simulation (e.g., PK, PD, and trial simulations) should use all of the information available and be an integral part of all pediatric development programs followed by verification using results from pediatric clinical studies. The following sections are critically important when developing the clinical pharmacology components of a pediatric study plan.

A. Approaches to Pediatric Studies

There are several recognized approaches to providing substantial evidence to support the safe and effective use of drugs in pediatric populations.[44] In some cases, previous data in adults and other pediatric indications can be leveraged to provide this substantial evidence. This concept is often referred to as pediatric extrapolation.

Pediatric extrapolation of efficacy is defined as an approach to providing evidence in support of effectiveness of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) populations.[45] Determination of the extent of pediatric extrapolation is predicated on the understanding of the disease and drug effect in the reference (adult or other pediatric) population and their similarity to the target pediatric

[44] For more information, see the FDA draft guidance entitled *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the Agency's current thinking on this topic.

[45] See the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018). See also 21 CFR 314.55(a).

population. The data necessary to support efficacy when pediatric extrapolation is considered will depend upon the existing data and the gaps in knowledge that should be addressed.[46] Examples of potential approaches based on the availability and confidence in existing data are discussed in sections 1 through 3 below.

While it is helpful and provides additional evidence to support extrapolation, formally establishing and documenting similarity in exposure-response in adults and target pediatric population is not a requirement in order to consider some degree of extrapolation. Exposure-response assessments are, however being conducted more frequently in both adult and pediatric patients. Knowledge of exposure-response, when available, can play a critical role in informing the assessment of drug effect similarity between adults and pediatric patients and the acceptability of an exposure-matching approach. In addition, exposure-response information can serve a crucial role in supporting pediatric dose selection, dose optimization and formulation development. When applicable, similarity in exposure-response relationships on a clinically relevant biomarker or an appropriate clinical endpoint can contribute to an assessment of the appropriateness of efficacy extrapolation from adults to pediatric patients.

Additionally, the extent of the required pediatric safety data can take into consideration prior experience with similar drugs in pediatric populations and the seriousness of the adverse events in adults or in pediatric populations. Usually, additional safety data in the indicated pediatric indication will be needed. See the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018) for more information. The potential for pediatric patients to have a significantly different incidence, severity, and types of adverse events compared to adults should always be considered.[47,48]

1. PK, Safety, and Efficacy Approach

If the disease or disease progression is unique to pediatric patients or its progression and/or response to intervention is undefined or dissimilar to that in adults, then the pediatric development program should use a PK, safety, and efficacy approach. The objectives of the studies in the pediatric program would be to characterize the PK and exposure-response relationships to help optimize pediatric dosing strategies and to provide evidence of effectiveness and safety. A population PK analysis can be conducted using PK data from the efficacy study to confirm PK estimates in the age subgroups.

---

[46] See the FDA guidance entitled *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) for more information.

[47] Liu XI, P Schuette, GJ Burckart, DJ Green, J La, JM Burnham, N Rakhmanina, A Robb, SM Huang, and JN van den Anker, 2019, A Comparison of Pediatric and Adult Safety Studies for Antipsychotic and Antidepressant Drugs Submitted to the US FDA, J Pediatrics, doi: 10.1016/j.jpeds.2018.12.033.

[48] Momper JD, Y Chang, M Jackson, P Schuette, S Seo, I Younis, DR Abernethy, L Yao, EV Capparelli, and GJ Burckart, 2015, Adverse Event Detection and Labeling in Pediatric Drug Development: Antiretroviral Drugs, Ther Inn Reg Sci, 49(2):302-309.

2. PK, Safety, and PD/Efficacy Approach

This approach should be considered when the disease and intervention are believed to behave similarly in pediatrics and adults, but the exposure-response relationship in pediatrics is either inadequately documented or assumed to not be sufficiently similar to adults. A clinically relevant PD biomarker may be appropriate for purposes of evaluating the evidence of effectiveness and to select pediatric doses. In the absence of a clinically relevant PD biomarker, clinical measures (e.g., symptoms, signs, outcomes) may be appropriate. The number, type, and size of pediatric studies to support a pediatric program depends on the residual uncertainty associated with understanding of similarity of the disease and drug effect.

For the two approaches described above, response data in pediatric studies should be collected and analyzed. Response or PD data can include biomarkers or clinical endpoints for both safety and effectiveness. The specific endpoints, including those for an exposure-response evaluation, for each drug should be discussed with the Agency. Appropriate endpoint selection and enrichment strategies for the pediatric population in a trial are important. Of note, endpoints that are unique to pediatric participants have been previously associated with failed pediatric trials and should be carefully considered.[49]

3. PK and Safety Approach

The PK and safety approach should be considered when there is evidence that adults and pediatrics share a sufficiently similar disease course and response to intervention to allow for exposure matching to establish efficacy.

A PK study should be performed to identify the pediatric dose that will provide an exposure similar to that found to be effective in adults. The antibacterial therapeutic area is a good example of this approach, where the organism is expected to respond to similar systemic concentrations in adults and pediatrics. In this example, the study should focus on identifying the doses in the pediatric setting that would result in exposures similar to those attained in adults. The criteria for determining exposure matching should be prospectively agreed upon with the Agency before initiating these studies.[50]

Before conducting a PK study in any of these approaches, simulations should be performed to identify initial dosing regimens. Clinical trial simulations may be performed to determine a trial design, sample size, and the appropriateness of an endpoint for the pediatric study. Refining models with available data can help verify assumptions made during the design of the study.

---

[49] Green DJ, J Burnham, P Schuette, XI Liu, BM Maas, L Yao, SK McCune, J Chen, JN van den Anker, and GJ Burckart, 2018, Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA, J Clin Pharmacol, 58(7):885-890.

[50] Mulugeta, Y, JS Barrett, R Nelson, AT Eshete, A Mushtaq, L Yao, N Glasgow, AE Mulberg, D Gonzalez, D Green, J Florian, K Krudys, S Seo, I Kim, D Chilukuri, and GJ Burckart, 2016, Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development, J Clin Pharmacol, 56(11):1326-1334.

B. Alternative Approaches to Conventional PK Studies

A dedicated PK study with intensive PK sampling may not be necessary in every age group. For example, prior experience with dosing in adolescent participants has demonstrated that knowledge of adult dosing and appropriate dose scaling can be sufficient for some drugs with adequate justification. When a dedicated PK study is not considered essential or cannot be conducted, it may be appropriate to use sparse PK sampling in the safety and/or efficacy studies to confirm dose predictions. Modeling and simulation can also be used, when appropriate, to help to fill these gaps in knowledge. See the FDA guidance entitled *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019) for more information.

Other approaches beyond the use of conventional PK studies with intensive blood sampling may be appropriate in pediatric participants to obtain useful drug exposure information, including:

- Sparse PK sampling with the use of modeling and simulation
- Opportunistic approaches that use excess blood collected for laboratory studies[51]
- Use of alternative specimens:
    - Urine and saliva collection are noninvasive. However, the interpretation of drug analyses of either source is complicated and requires careful consideration before use.
    - Likewise, tissue or cerebrospinal fluid collected for clinical purposes present both an opportunity and a challenge for the appropriate interpretation of these results in understanding the pharmacokinetics of the drug.

Modeling and simulation can help reduce the uncertainty about drug dosing in pediatric populations. Model-informed drug development has been applied in regulatory applications for pediatric drug development.[52] Population PK approaches are commonly used, and physiologically based PK (PBPK) approaches are increasingly applied in pediatric drug development. In addition, quantitative systems pharmacology (QSP) models can help

[51] For more information, see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

[52] Bi, Y, J Liu, L Li, J Yu, A Bhattaram, M Bewernitz, R Li, C Liu, J Earp, L Ma, L Zhuang, Y Yang, X Zhang, H Zhu, and Y Wang, 2019, Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling, J Clin Pharmacol, 59(S1):S104-S111.

incorporate disease processes.[53,54] As science and technology continue to advance, in silico and other alternative modeling study methods can provide preliminary data to inform the design and conduct of PK-PD studies for investigational drugs in pediatric populations. For example, the development of a PBPK in silico model that integrates drug-dependent parameters (e.g., physicochemical properties, hepatic intrinsic clearance, affinities to metabolic enzymes, transporters, and proteins) and system- and age-dependent parameters (e.g., blood flow rate, protein contents, tissue and organ size and composition, and enzyme and transporter abundances and activities) is one possible approach.

Various modeling approaches have been used in pediatric drug development programs for a variety of purposes, including:

- Planning for a first-in-pediatric PK study
- Optimizing the study design
- Verifying the model in specific age groups
- Recommending starting doses
- Informing enzyme ontogeny using a benchmark drug
- Facilitating covariate analysis for the effects of organ dysfunction or drug interactions in pediatric participants[55]

The model selected should incorporate in vivo PK-PD data obtained in other groups of pediatric and adult participants as well as human volunteer studies, as appropriate. To account for growth across the pediatric population for modeling purposes, refer to standardized growth charts. The Centers for Disease Control and Prevention (CDC) growth charts provide a preliminary assessment of the weight ranges that can be anticipated within specific age groups.[56] For example, weights can vary 2.5- to 3-fold in healthy children between the 10th percentile at 2 years and 90th percentile at age 6 (10.6 kg to 25.3 kg for males) and between the 10th percentile at

---

[53] Momper, JD, GJ Burckart, and P Jadhav, 2013, Applications of Population Pharmacokinetics for Pediatric Drug Development, Pediatric Drug Development: Concepts and Applications, AE Mulberg, D Murphy and LL Mathis, Chichester, UK, John Wiley & Sons Ltd.

[54] Wang, J, AN Edginton, D Avant, and GJ Burckart, 2015, Predicting Neonatal Pharmacokinetics From Prior Data Using Population Pharmacokinetic Modeling, J Clin Pharmacol, 55(10):1175-1183.

[55] Leong, R, MLT Vieira, P Zhao, Y Mulugeta, CS Lee, SM Huang, and GJ Burckart, 2012, Regulatory Experience With Physiologically Based Pharmacokinetic Modeling for Pediatric Drug Trials, Clin Pharmacol Ther, 91(5):926-931.

[56] Centers for Disease Control and Prevention, National Center for Health Statistics, 2000 CDC Growth Charts for the United States: Methods and Development (May 2002), available at: http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf (Accessed September 17th, 2019).

6 years and the 90th percentile at 12 years (17.7 kg to 54 kg in males). Caution should be taken in the use of standardized growth charts as they do not always represent the target pediatric patient population.

C. Pediatric Dose Selection

Selecting a dose(s) and an age range should consider the overall benefit/risk profile of the drug. When possible, a range of doses should be studied in the pediatric population.

Factors for consideration in dose selection include:

- The similarity of the disease and exposure-response in pediatric and adult groups
- The relative bioavailability of the new formulation compared to the previous formulations
- The age and developmental stage of the pediatric population
- Any pharmacogenomic characteristics of the drug
- The toxicity of the drug
- Any PK data from other pediatric populations

Because there can be limited information on the safety of the dose to be administered to a neonate or infant, the dose range used in initial studies requires careful consideration.[57] When developmental maturation and body size changes impact dosing, modeling and simulation can help define an initial pediatric dosing in order to adequately minimize the risk for specific age groups. Initial doses within a pediatric age group are typically normalized to body size (e.g., mg/kg), but developmental maturation can be an additional critical factor to be considered in establishing initial doses in some age groups. In some pediatric participants such as adolescents, body weight or surface area-based dosing are not always necessary. In some cases, final dosing recommendations can include tiered dosing based on weight bands.

There are situations in which interpolation or scaling can reduce the uncertainty regarding initial pediatric dosing. PK or PD information in certain pediatric age groups can be gained by interpolating or bridging from existing data in adults, pediatric participants in other age groups, or both. However, bridging of data to younger pediatric age groups, particularly neonates, should be done cautiously and confirmed. Significant developmental differences that can exist between young pediatric age groups and older pediatric age groups or adults are associated with considerable differences in metabolism and drug disposition. This difference can lead to an altered dose-exposure relationship and therefore the dose-response relationships.

[57] For more information, see the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022).

When initial PK studies are not feasible (see section IV), an adaptive design to selecting a dose can be practical for the pediatric clinical studies. Adaptive designs should be prospectively determined. See the FDA guidance entitled *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018) for more information.

When separate efficacy studies in pediatrics are not conducted (i.e., for the *PK and safety only* approach described in section V.A above), in general, PK studies in the pediatric population should determine how the dosage regimen should be adjusted to achieve the same level of systemic exposure in adults. Differences in intersubject variability in these PK measures and/or parameters between age groups or between pediatric and adult populations should be interpreted with regard to their impact on dosing, safety, and/or efficacy. In these instances, the sponsor should pre-specify the criteria by which exposure matching is acceptable. For example, one approach is to select the appropriate dosing strategy through simulations which result in pediatric exposures within the 5th to 95th percentile shown to be safe and effective in adults.

Estimating the exposure-response relationship across a range of body-size doses (dose/kg or dose/m^2) can be important. For the *PK and PD/efficacy* approaches discussed in section V.A2 above, investigating a range of doses and exposures allows for an assessment of those relationships and the development of rational dosing instructions. The sponsor should also consider determining the variability in achieved systemic exposures in the pediatric population in the context of the exposure-response relationships for pharmacodynamics or efficacy.

When PK-PD data are available, the dose range should account for observed differences in response between adults and the pediatric population, both in terms of exposure and response. For example, there is evidence that pediatric populations are on average less sensitive to antihypertensive drugs than the adult population.[58] Therefore, pediatric studies could include exposures greater than the highest drug exposure associated with the approved adult dose, provided that prior data about the exposure-response relationship and safety information justify such an exposure. Studies of distinctly different ranges of exposure are desirable to provide sufficient information for the calculation of an optimal dose.

D. Pediatric Dosage Formulation

Pediatric formulations that permit accurate dosing and enhance adherence (e.g., palatability) are an important part of pediatric drug development.[59] See the FDA guidance entitled *E11 Clinical*

[58] Benjamin, DK, Jr, PB Smith, P Jadhav, JV Gobburu, MD Murphy, V Hasselblad, C Baker-Smith, RM Califf, and JS Li, 2008, Pediatric Antihypertensive Trial Failures: Analysis of End Points and Dose Range, Hypertension, 51(4):834-840.

[59] Refer to the FDA draft guidance entitled *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018) for information on the use of liquids and/or soft foods for drug administration. When final, this guidance will represent the Agency's current thinking on this topic. In addition, refer to the following FDA guidances for more information on assessing the bioavailability and effect of food on a new formulation: *Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations* (June 2022) and *Bioavailability Studies Submitted in NDAs or INDs - General Considerations* (April 2022).

Investigation of Medicinal Products in the Pediatric Population (December 2000) for more information. If there is a pediatric indication, an age-appropriate dosage formulation must be made available for pediatric patients in all relevant age groups.[60] One way to fulfill this requirement, when the adult formulation is not acceptable for the planned pediatric age range, is to develop and test a pediatric formulation and seek approval for that formulation. To the extent practicable, sponsors should include information in the iPSP regarding planned excipients that will be contained in a pediatric formulation.

The bioavailability of any formulation used in pediatric studies should be characterized in relation to the adult formulation. In some circumstances, a relative bioavailability study comparing the age-appropriate formulation to the approved drug may be required.[61] These studies are generally performed in adults due to ethical reasons. Potential drug-food or vehicle interactions should be considered, such as those that have been reported with apple juice.[62]

E. Sample Size

1. Number of Pediatric Participants

Prior knowledge of the disease, exposure, and response from adult and other relevant pediatric data, such as that related to variability, can be used to derive a sample size for ensuring precise parameter estimation. The sponsor should account for all potential sources of variability, including inter-subject and intra-subject variability as well as differences between the adult and pediatric populations when making the final selection of the sample size for each age group.

The distinct age groups to be studied should be chosen based upon what is known about potential changes in drug response with age, the development of the drug-metabolizing enzymes and excretory mechanisms, as well as safety considerations. Pediatric studies in all age groups should be initiated as early as possible in drug development. The sequential study of age cohorts, starting with the oldest pediatric age group, may be appropriate when there is a clear rationale for doing so. If the drug is intended to be used in newborn infants, the iPSP should specify how premature infants will be considered in the study population.

Because the selected age groups (strata) will be drug product-specific, the sponsor should discuss the stratification plan, the distribution of the number of pediatric participants within each stratum, and the appropriateness of these strata with the Agency.[63] Justification should be provided for the sample size selected. For example, one approach would be to prospectively

---

[60] See section 505B(a)(2) of the FD&C Act, 21 U.S.C. 355c(a)(2).

[61] 21 CFR 320.21.

[62] Abdel-Rahman, SM, MD Reed, TG Wells, and GL Kearns, 2007, Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: Avoiding the Problems and Pitfalls, Clin Pharmacol Ther, 81(4):483-494.

[63] McMahon, AW, K Watt, J Wang, D Green, R Tiwari, and GJ Burckart, 2016, Stratification, Hyopthesis Testing, and Clinical Trial Simulation in Pediatric Drug Development, Ther Inn Regu Sci, doi: 10.1177/2168479016651661.

target a 95 percent confidence interval within 60 percent and 140 percent of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric stratum with at least 80 percent power. Noncompartmental analysis (NCA) based on rich PK sampling, population PK modeling analysis based on sparse PK sampling, or other scientifically justified methods can be applied as appropriate to achieve this precision standard.[64]

Conceivably, certain disease states might not allow for the recruitment of an adequate number of participants to meet the above standard, and as such, practical considerations should be taken into account in determining the sample size.

2. Number of Samples Per Participant

In addition to the number of participants, the number of blood samples collected in the clinical pharmacology study to estimate PK measures and parameters for each individual in the study should be carefully considered. The amount of blood or number of samples possible is very limited in some pediatric participants such as neonates (for more on collection of blood or plasma samples, see section F below). Clinical trial simulations and optimal sampling strategies are recommended to justify the proposed sampling scheme.

F. Sample Collection

The volume and frequency of blood sampling are often of concern in pediatric studies. Blood samples can be obtained by direct venipuncture, through the use of an indwelling intravascular catheter, or when appropriate, by capillary sampling. Because repeated venipuncture can cause discomfort and bruising at the puncture site, an indwelling intravascular catheter should be used when possible. The volume and frequency of blood sampling may be minimized by using micro-volume drug assays, dried blood spots, and sparse-sampling techniques. See the FDA guidance entitled *Bioanalytical Method Validation* (May 2018) for more information. These types of assays and analysis are especially relevant when studying neonates.[65] Modern assay techniques allow small sample volumes to be used to determine drug concentrations, but data quality can be affected if the sample volume is insufficient to allow for reanalysis when necessary. Blood samples for analysis should be collected from the circulating blood volume and not from reservoir dead space created by catheters or other devices. Sampling technique is critical when using the available pediatric indwelling intravenous catheters. The time of sample collection, proper sample transportation and storage, and sample handling techniques should be documented. The collection of fluids such as cerebral spinal fluid (CSF) or bronchial fluids can be beneficial when samples are being obtained for clinical purposes. Noninvasive sampling procedures, such as urine and saliva collection, may be sufficient if correlated with outcomes or if the correlation with blood, serum or plasma levels has been documented.

[64] Wang, Y, PR Jadhav, M Lala, and JV Gobburu, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52:1601-1606.

[65] Long, D, G Koren, and A James, 1987, Ethics of Drug Studies in Infants: How Many Samples are Required for Accurate Estimation of Pharmacokinetic Parameters in Neonates?, J Pediatrics, 111(6Pt1):918-921.

Samples for DNA should be collected when appropriate, as discussed in section III of this guidance. See also the FDA guidance entitled *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (January 2013) for more information.

G. Covariates and Phenotype Data

Growth and developmental changes in the pediatric population create substantial changes in the ADME characteristics of a drug. PK measures and parameters for a drug should be described as a function of age and be related to some measure of body size, such as height, weight, or body surface area (BSA). The maturational changes in systems affecting ADME, such as membrane transporters and metabolizing enzymes, should be considered when choosing age groups and doses to study in the pediatric population (see section III).

The sponsor should, at a minimum, obtain the following covariates for each pediatric participant:

- Age
- Body weight
- Height
- Calculated BMI
- Gestational age
- Post-menstrual and postnatal age for neonates[66]
- Race and ethnicity
- Sex
- Laboratory tests reflecting the function of organs responsible for drug elimination
- Concomitant and recent drug therapy

The impact of the disease state and obesity upon drug disposition and response should be considered.[67] Sponsors are encouraged to collect DNA samples in pediatric PK studies under the circumstances described in section III, along with appropriate phenotype information to optimize the interpretation of pharmacogenomics findings. For example, when genotype information is obtained for a cytochrome P450 enzyme, the sponsor should investigate the influence of genetic mutations on pharmacokinetics, pharmacodynamics, and/or dose-response to determine whether genetically defined subsets of patients need special dosing considerations.

The sponsor should examine the relationship between the covariates and the pharmacokinetics of the drug of interest. The contribution of weight or BSA and age to PK variability should be assessed. Examples of practices for assessing the effect of age on pediatric pharmacokinetics could include:

[66] See the FDA guidance entitled *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products* (July 2022) for more information.

[67] Vaughns JD, LS Conklin, Y Long, P Zheng, F Faruque, D Green, J van den Anker, and GJ Burckart, 2018, Obesity and Pediatric Drug Development, J Clin Pharmacol, doi:10.1002/jcph.1054.

- Identifying the accurate relationship between a drug's pharmacokinetics and body weight or BSA using allometric scaling

- Analyzing the residuals versus age, after accounting for body weight or the BSA effect on CL, followed by a more formal analysis exploiting the physiological understanding underlying CL, if appropriate. Testing for other biologically relevant predictive factors for determining the pharmacokinetics of a drug in pediatrics can be important. The covariate analysis may be performed on pooled data sets to allow for comparisons between adults and/or different pediatric subgroups.

1. Immunogenicity

The pharmacokinetics of a drug such as therapeutic proteins can be affected by immunogenicity to the drug. Immunogenicity to the administered product can negatively impact the safety and/or efficacy of the drug. Therefore, assessing the immunogenicity of the relevant drugs and determining its impact on pharmacokinetics, safety, and efficacy are critical components of drug development and post-marketing surveillance. See the following FDA guidances for more information:

- *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

- *Immunogenicity Testing of Therapeutic Protein Products - Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019)

In general, it is not appropriate to apply findings of the immunogenicity potential of a drug from adult populations to pediatric populations; therefore, evaluation of the immunogenicity potential of a drug should be conducted in pediatric trials regardless of the knowledge gained from adult trials.

2. Renal Function

For drugs that are renally cleared, exposures can be impacted by both the maturation of kidney function and renal impairment due to kidney disease. For this reason, pediatric patients with impaired renal function should be recruited for clinical study when it is possible and ethically justifiable to do so. One commonly used equation for the estimation of renal function is the bedside Schwartz equation;[68] however, in general any widely accepted measurement method (where necessary) or equation for the estimation of renal function in pediatric PK studies is acceptable[69] and should be described in the protocol and labeling when relevant dose

[68] Schwartz, GJ, A Munoz, MF Schneider, RH Mak, F Kaskel, BA Warady, and SL Furth, 2009, New Equations to Estimate GFR in Children with CKD, J Amer Soc Nephrol 20(3):629-637.

[69] Muhari-Stark E and GJ Burckart, 2018, Glomerular Filtration Rate Estimation Formulas for Pediatric and Neonatal Use, J Pediatr Pharmacol Ther, 23(6):424–431.

adjustments are derived. Sponsors should be aware of the laboratory methods used for the measurement of creatinine, as this can influence which equation is useful.

Data from adults are generally used to complement the information obtained in pediatrics to characterize the relationship between renal function and pharmacokinetics. Modeling and simulation approaches should be applied to derive dosing recommendations for the entire pediatric age range in which the product will be used.[70] Generally, for children over the age of 2 years, where kidney function maturation is considered complete, the need for dose adjustment should be evaluated and derived based on information evaluated in adults. For children less than 2 years of age, the additional impact of renal function ontogeny should be considered.[71] Quantitative approaches such as PBPK analysis can also be explored to address dosing needs in these situations. Of note, the application of modeling is limited by current understanding of ontogeny and is particularly challenging in neonates. However, modeling approaches should use all of the clinical information available.

H. Drug-Drug Interactions

In general, evaluations of drug-drug interactions (DDIs) are performed in adults. In some cases, however, the potential or magnitude of a DDI in pediatrics can differ from that observed in adults. Such differences in DDIs in pediatrics compared to adults can potentially be attributed to the ontogeny of metabolizing enzymes and transporters as well as differences in intragastric pH, gastric emptying, intestinal motility, or protein binding. Differences in diet, concomitant medications, drug formulation, and dosing regimen could also contribute to differences in DDIs between adults and pediatrics.[72]

Considering potential ethical concerns for standalone DDI studies in pediatrics, quantitative approaches such as PBPK analyses should be explored to address pediatric DDIs during drug development when differences in DDI are expected. Refer to the following FDA guidances for more information:

- *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)

- *Physiologically Based Pharmacokinetic Analyses — Format and Content* (September 2018)

[70] For information on studying trial participants with impaired renal function, see the FDA draft guidance entitled *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (September 2020) for general concepts of study design. When final, this guidance will represent FDA's current thinking on the topic.

[71] Zhang Y, N Mehta, E Muhari-Stark, GJ Burckart, J van den Anker, L Yao, and J Wang, 2019, Pediatric Renal Ontogeny and Applications in Drug Development, J Clin Pharmacol, 59(S1):S9-S20.

[72] Salerno, SN, GJ Burckart, SM Huang, and D Gonzalez, 2019, Pediatric Drug-Drug Interaction Studies: Barriers and Opportunities, Clin Pharmacol Ther 105(5):1067-1070.

Planning for DDI evaluations should be included as a section of the iPSP under Pediatric Pharmacokinetic Studies and should address the impact of DDIs on drug dosing in specific age groups. See the FDA guidance entitled *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (July 2020) for more information.

I. Sample Analysis

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the drug and metabolites in the biological fluids of interest is essential. See the FDA guidance entitled *Bioanalytical Method Validation* (May 2018) for more information. The sponsor should choose a method that is readily adaptable and uses only minimum sample volumes.

J. Data Analysis

The development of PK models should occur throughout the pediatric development program. All prior knowledge, including adult data, should be used to develop initial models which can be adapted as new data become available in pediatric subgroups. There are several basic approaches for performing PK analysis in pediatrics. Population PK and noncompartmental PK approaches are two of the most commonly used; however, novel approaches may be acceptable as justified by the sponsor.

1. Population Analysis

A common approach for analyzing data from pediatric clinical pharmacology studies is the population approach to PK analysis. Population PK accommodates rich (intensive) and infrequent (sparse) sampling of blood, serum, or plasma from a larger population than in a compartmental or noncompartmental analysis PK approach to determine the PK parameters. Sparse sampling is generally considered more acceptable for pediatric studies because the total volume of blood sampled in an individual can be minimized. Sampling can even be performed concurrently with clinically necessary blood or urine sampling (e.g., opportunistic PK studies). Because relatively large numbers of pediatric participants are studied, and samples can be collected at various times of the day and repeated over time in a given participant, 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. See the FDA guidance entitled *Population Pharmacokinetics* (February 2022) for more information.

Exposure-response analyses predominantly employ a population analysis approach. Individual analysis is generally not recommended unless responses from a wide range of doses from each participant are available. Modeling of data across all study participants typically provides the best opportunity to describe the exposure-response relationship. See the FDA guidance entitled *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* for more information (May 2003).

2. Noncompartmental Analysis

If consistent with relevant ethical considerations (see Section IV: Ethical Considerations), it may be possible to utilize intensive PK sampling with relatively frequent blood and urine sample collection, when administering either single or multiple doses of a drug to a relatively small group of study participants. Samples are collected over specified time intervals chosen on the basis of absorption and disposition half-lives, and subsequently assayed for either total or unbound concentrations of drug and relevant metabolites. Noncompartmental analysis is a general approach to establish PK statistics and parameters such as AUC, C_{max}, CL, volume of distribution, and half-life, which are descriptive of the concentration of drug or metabolite over time. Data are usually expressed as the means of the relevant measure or parameter and inter-individual variances. In this approach, including a sufficient number of study participants to give a precise estimate of the mean is essential, as discussed in section V.E. If drug administration and sampling are repeated in a participant in the PK study, some understanding of intra-individual variability in PK parameters can be obtained.

K. Clinical Study Report

The clinical study report should follow the FDA guidance entitled *E3 Structure and Content of Clinical Study Reports* (January 2013) for the general content and the format of the pediatric clinical study report. The evaluation of exposure-response relationships and the population PK analyses should be included as stipulated in the following FDA guidances:

- *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications* (May 2003)

- *Population Pharmacokinetics* (February 2022)

When submitting PK information, the sponsor should submit data that illustrate the relationship between the relevant PK parameters (e.g., CL unadjusted and adjusted for body size in the manner described in section VI.G) and important covariates (e.g., age, renal function) in addition to the results of noncompartmental analysis.

L. Data Submission

The preferred submission standard for clinical data is the Clinical Data Interchanges Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard. Please see the FDA Data Standards Advisory Board[73] and the CDER Study Data Standards web sites for more information.[74] The sponsor should also submit PK and exposure-response data used for modeling and simulation in an SAS.XPT-compatible format.

[73] See the FDA Data Standards Advisory Board, available at: https://www.fda.gov/industry/fda-resources-data-standards.

[74] See the FDA Study Data Standards for Submission to CDER, available at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber.